Achieving Sterility in Medical and Pharmaceutical Products

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Sterilization by Ethylene Oxide

Of the several methods of sterilization that rely on inactivation of microorganisms to meet their objective, sterilization by exposure to ethylene oxide is by far the most difficult to control. The main advantages of ethylene oxide as a sterilant do not lie in speed, simplicity, or reliability of control but rather in the range of materials that can withstand treatment without damage. It is not used for pharmaceuticals. It is, however, an extensively used alternative to irradiation as

a method of cold sterilization for heat-labile medical devices and pharmaceutical packaging components. Industrial-scale and laboratory-scale technologies are available.

Ethylene oxide is a cyclic ether (C_2H_4O) with a boiling point of 10.7°C at atmospheric pressure. It is colorless and virtually odorless. In its pure form ethylene oxide is highly flammable in air; in particular circumstances it may be explosive. Its first practical application as a biocide was as recently as the 1940s when it began to be used for disinfestation of food crops. It is still used to reduce the microbial contamination of bulk spices. As with gamma radiation, its development as a sterilization process for medical devices went hand in hand with the increased availability of biologically inert plastics. Until radiation sterilization became competitive in the 1960s and 1970s, it was the single most important method of industrial-scale cold sterilization. In terms of volume of items sterilized it has now been overtaken by irradiation, partly because of simple economic reasons and partly because it has been found to be carcinogenic.

I. INACTIVATION EFFECTS ON MICROORGANISMS AND MICROBIAL POPULATIONS

Inactivation and death of microorganisms results from alkylating effects on sulfhydryl, amino, carboxyl, and hydroxyl groups within the cell. Ethylene oxide replaces labile hydrogen atoms in these groups. Lethal effects are through blockage of reactive sites on metabolically active molecules. Comparison of activation energies has shown that DNA and RNA are the most likely target molecules. Unlike most other chemical sterilants, which are several thousand times more active against vegetative cells than spores, the resistance of spores to ethylene oxide and other alkylating agents is less than ten times greater than the resistance of vegetative organisms. For instance, spores of *Bacillus stearothermophilus* and *Clostridium sporogenes* have been shown to show a very similar response to vegetative cells of *Streptoccus faecium* when exposed under identical conditions [1].

The kinetics of inactivation of microbial populations exposed to ethylene oxide are exponential [2] when the logarithm of the number of survivors is plotted against time with all other factors (e.g., gas concentration, humidity, temperature) held constant. Shouldered curves have been occasionally noted; instances of "tailed" inactivation kinetics have been ascribed to clumping or environmental protection. Good experimental data are not easily obtained. Experimental design should concentrate on rapid attainment of the gas concentration intended. Inactivation from residual sterilant may also lead to misleading results.

D-values have only a very limited value for comparing the resistance of various microorganisms and various ethylene oxide processes. This is because inactivation characteristics are subject to the influence of numerous other vari-

ables that are unavoidably part of ethylene oxide sterilization technology. The complexity of interaction between gas concentration, temperature of exposure, humidity during exposure, pressure during exposure, and the condition of the microbial population prior to exposure has not been adequately described by theory.

A. Effects of Gas Concentration on Microbial Response to Ethylene Oxide

The effects of the concentration of ethylene oxide on inactivation of microorganisms are quite straightforward. Within limiting concentrations, the effect of doubling the gas concentration doubles the rate of inactivation. Concentrations of less than 300 mg/L are insufficient to achieve sterility within practical process times. Very high gas concentrations imply very high pressures, and the gas laws dictate that an increase in temperature is necessary within a sterilizer at constant volume to maintain equilibrium conditions at increased pressures, possibly too high a temperature to meet the intended cold sterilization purposes. In practice, gas concentrations are usually within a range of 500 to 800 mg/L, which is a practical compromise among sterilization effectiveness and process time and for the constraints imposed by available technology.

B. Effects of Temperature on Microbial Response to Ethylene Oxide

Alkylation reactions respond to temperature in the same way as normal chemical reactions. Under constant conditions and within the range of limiting gas concentrations, ethylene oxide sterilization follows first-order chemical kinetics, i.e., the rate of inactivation is approximately doubled (the *D*-value is halved) for every 10°C rise in temperature. The lowest temperature at which ethylene oxide sterilization is theoretically possible is the temperature at which the gas liquefies, which is 10.7°C at atmospheric pressure. Upper limits of temperature are of less importance, because the whole point of using ethylene oxide is to achieve cold sterilization. Other restricting factors at high temperatures are polymerization and the pressure rating of ethylene oxide sterilizers. Industrial-scale processes normally operate within a cold sterilization range of 50 to 60°C.

C. Effects of Humidity on Microbial Response to Ethylene Oxide

Humidity is the single most important factor influencing the effects of ethylene oxide on microbial populations. Ethylene oxide is quite simply ineffective against dehydrated microorganisms in a dry environment.

Ethylene oxide is a chemical sterilant and must therefore come into contact with target molecules (DNA and RNA) that are physically located within the "heart" of the cell, or within the core of bacterial spores. Water acts as a carrier of ethylene oxide through permeable barriers. The water activity of the micro-

bial cell and the relative humidity of the environment in which it finds itself are of critical importance to water movement and to the penetration of chemical sterilants to their target sites. The situation becomes complex when it is understood that ethylene oxide can itself increase the permeation of water through permeable barriers.

Most experimental work on the effects of humidity has been done on bacterial spores. Bacterial spores can survive over a greater range of water activities and moisture contents than vegetative cells. In particular they can withstand considerable degrees of desiccation. Although spores are not actively dividing microorganisms, they are not completely metabolically inactive. Ernst and Doyle [3] postulated that dynamic equilibria exist between spores and their immediate environment, determined in the main by the number and types of active sites on the surfaces of the spores. Active sites become physically withdrawn from the surfaces as the spores dehydrate. Spores with higher moisture contents and therefore greater numbers of exposed active sites exhibit higher rates of exchange of molecules with their immediate environment than do dry spores with low water activities.

The equilibrium between the spore and the environment can operate in two directions, i.e., with water moving predominantly from the environment into the spore or conversely predominantly out of the spore into the environment. The direction of the equilibrium as it affects water movement is for the most part a function of the relative humidity of the environment. With relatively high environmental moisture, water will move into the spore. The concentration gradient between the moisture content of the spore and the moisture content of the environment acts as a driving force in accord with Fick's laws of diffusion. At low environmental relative humidities water will move out of the spore into the environment.

The significance of this model is that it describes the optimal situation for water permeation into the spore and therefore ethylene oxide permeation to its target site as a function of the moisture content of the spore and the relative humidity of the environment during exposure. The rate of microbial inactivation therefore increases (as long as all other factors are held constant) with increased relative humidity during exposure. Kaye and Phillips [4] demonstrated a 33% RH optimum for microbial inactivation as a result of exposure to ethylene oxide. In practical situations it is better to err on the side of too much rather than too little moisture. With industrial-scale ethylene oxide sterilization, humidity levels are usually in the range of 50% to 60% RH. The upper limit is usually dictated by deleterious effects on packaging.

D. Other Factors Affecting Microbial Response to Ethylene Oxide

Any factor that prevents permeation of ethylene oxide to its target sites within the cell is capable of adversely influencing the rate of inactivation. Such factors

may include organic matter or inorganic crystalline material. Reduced sterilant penetration has also been noted with clumped cells. These effects are probably due as much to physical factors as to chemical ones. Although ethylene oxide has a history of use as a crude fumigant, it is suitable as a sterilant only for clean items, which components for pharmaceutical products and medical devices can always be supposed to be when manufactured according to the Good Manufacturing Practices.

Dadd and Daley [5] observed that some microorganisms may have a limited ability to overcome the effects of ethylene oxide but that this did not to any great extent confer resistance. The spore coat did not contribute to the resistance of resistant bacterial spores except as it constituted an increased number of alternative target sites for alkylation. Spores did not become as sensitive to ethylene oxide as vegetative cells until they had fully emerged from inside their spore coats.

II. APPLICATIONS OF ETHYLENE OXIDE STERILIZATION

Ethylene oxide sterilization is suitable for both small-scale and large-scale applications. It is primarily a method of cold sterilization and has so many associated complications that it is never used in preference to thermal sterilization for heat-stable materials. Sterilization by gamma radiation is more reliable than ethylene oxide for cold sterilization, and it is simpler to control. It is, however, limited by suitability of materials and only operates on a large scale.

Ethylene oxide is penetrative (but less penetrative than gamma radiation). On an industrial scale this allows devices sealed within primary containers to be packed into shelf packs or shippers and palletized before sterilization. Product is normally sterilized on pallets.

In order to inactivate microorganisms, ethylene oxide must come into contact with target sites in the microbial cell. Even though ethylene oxide is very penetrative, this is a major complicating factor for any method of terminal sterilization. Free movement of the gas to all parts and internal cavities of each item being sterilized is an essential prerequisite of the process. This imposes certain constraints (arguably restrictive constraints in the case of individually packed single-use medical devices) on the design of product items, the design of packaging materials, the choice of packaging materials, and the manner in which products are packed in boxes, stacked, palletized, and loaded into sterilizers.

A basic prerequisite of product design is that sealed internal cavities should be avoided for products intended for terminal sterilization by exposure to ethylene oxide. Disposable hypodermic syringes were among the first medical devices to be sterilized in large numbers by ethylene oxide. Syringe plungers are usually fitted with elastomeric tips that seal with an interference fit to the internal barrel wall at two diameters separated by an internal cavity (Fig. 1). The

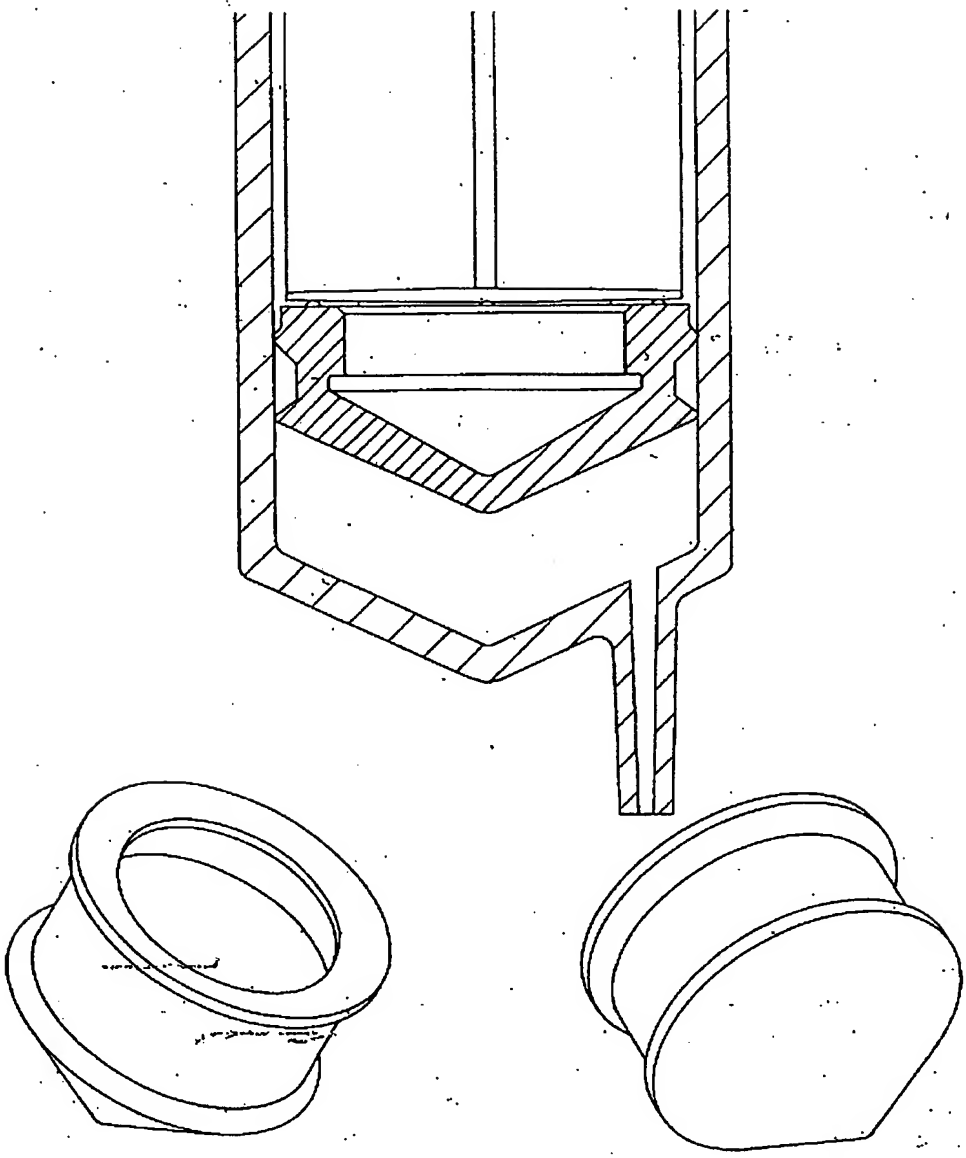

Fig. 1 Internal cavities in hypodermic syringes.

region between the two "lands" of the plunger tip is usually considered the most difficult to sterilize because of uncertainty concerning gas penetration. Although this region is strictly a sealed cavity, ethylene oxide may gain access if the plunger tip is made from a gas-permeable material. While natural rubber remains the commonest material for manufacture of plunger tips, the ready absorption of ethylene oxide into this material prevents poor penetration from

restricting gaseous sterilization of syringes. However, other elastomeric materials, which may not be as permeable to ethylene oxide, are becoming competitive with rubber and are beginning to offer advantages in the areas of materials costs and consistency of quality.

Penetration is important to the selection of packaging materials where these are the primary barrier to microbiological contamination of the device after sterilization and before use. Most often, cold-sterilized medical devices are packed in flexible rather than rigid primary containers. Permeable materials are necessary when ethylene oxide is the method of sterilization. Paper is commonly used because it has a history of successful usage, because the technology for printing on paper is readily available, and because it is cheap and recyclable. On the other hand, it is not always impermeable to microorganisms; it is opaque, and it may tear easily on devices with sharp edges or when subjected to pressure differentials or when carelessly handled or transported. Alternative permeable materials that avoid the disadvantages of paper, such as spun-bonded polyolefins (Tyvek), are very expensive. Almost any material can be sealed to any other material, and therefore composite packs made from more than one material are common. One part of the pack may be gas permeable, the other impermeable, one part opaque and printable, the other transparent. The technology of ethylene oxide sterilization involves high humidities and pressure changes. The potentially deleterious effects of these aspects of the sterilization processes on seal integrity are not insignificant.

With some other medical devices, only the sterility of the internal lumina (fluid path sterility) is being claimed. Typically these devices are sealed and self-contained without any primary packaging. Some drug delivery systems, for instance, are sealed at their ends, and fluid path sterility only is being claimed. Self-contained sterile insulin syringes are one of the largest bulk volume sterile medical devices in the world. With these devices it is necessary to vent the caps or seals to allow access of ethylene oxide. This creates a clear conflict with the requirement for hermetic sealing of the sterilized device against entry of microorganisms.

One way of resolving this has been to ensure that any venting is achieved only through sterilant-permeable antimicrobial filters. Alternatively, vent caps may be designed to have a small unfiltered tortuous passage to the exterior that can be demonstrated empirically to make entry of the microorganisms into the fluid path improbable. Before adopting such designs, manufacturers should address the choice of ethylene oxide versus other methods of cold sterilization. With radiation sterilization, for instance, venting is not necessary.

III. ETHYLENE OXIDE STERILIZATION PROCESSES

Ethylene oxide is a product of the petroleum industry primarily produced as a starting material for polyethylene glycol (antifreeze) and other related sub-

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stances. For sterilization purposes it is commercially available in the pure form or as mixtures with fluorinated hydrocarbons or carbon dioxide. Pure ethylene oxide is highly flammable in air. In sterilization it is normally used in conjunction with an inert gas such as carbon dioxide or nitrogen from a separate source. Commercially available gas mixtures are nonflammable under normal operating conditions of temperature and pressure. Mixtures of 12% ethylene oxide : 88% dichlorodifluoromethane, and 20% ethylene oxide : 80% carbon dioxide have been commonly used. Environmental issues relating to the use of fluorinated hydrocarbons are seriously restricting the use of so-called 12:88.

Pure ethylene oxide is cheaper than gas mixtures. At one time it was used undiluted, but it is no longer possible to have this practice underwritten for insurance purposes. All existing processes, whether using pure ethylene oxide plus a diluent or using a gas mixture, operate at a positive pressure to the atmosphere. Any leakage of gas from the chamber must therefore be toward dilution in the external environment rather than toward formation of an explosive mixture in the chamber. Gas mixtures with fluorinated hydrocarbons or carbon dioxide require higher operating pressures to achieve the same sterilant concentrations as diluted pure ethylene oxide systems.

Industrial-scale ethylene oxide sterilization usually takes place in steel pressure vessels (Fig. 2) equipped with water or steam jackets to maintain the operating temperature within reasonable tolerances throughout the sterilization process or cycle. Intrinsically the equipment is no more elaborate than that used for steam sterilization except that the vessels are often considerably larger. Ethylene oxide sterilizers with capacities of greater than 1,000 ft^3 (eight or ten pallets) are not uncommon. Essential features include some means of evacuating the chamber to facilitate the introduction of ethylene oxide and steam, and some means of vaporizing (usually a heat exchanger) the ethylene oxide that exists in its liquid phase in pressurized cylinders or drums.

Pure ethylene oxide for use in conjunction with a diluent gas and 20:80 mixtures of ethylene oxide are potentially explosive; all electrical equipment, switchgear, and monitoring and measuring systems used in association with these forms of the sterilant must be sparkproof. Serious consideration should be given to the location and design of gas stores and sterilization suites in relation to other areas within a factory, in relation to other factory buildings, and in relation to the local community. Blow-out roofs, windows, and walls are commonly installed with the intention of channelling the shock waves from an explosion in the direction of least harm.

The internal construction of ethylene oxide sterilizers is uncomplicated and uncluttered. There may be some form of forced air circulation to prevent stratification of the various types of gas present in the chamber during sterilization (sterilant, diluent, moisture). There should be the devices or sample ports for continuous monitoring and recording of temperature and pressure within the

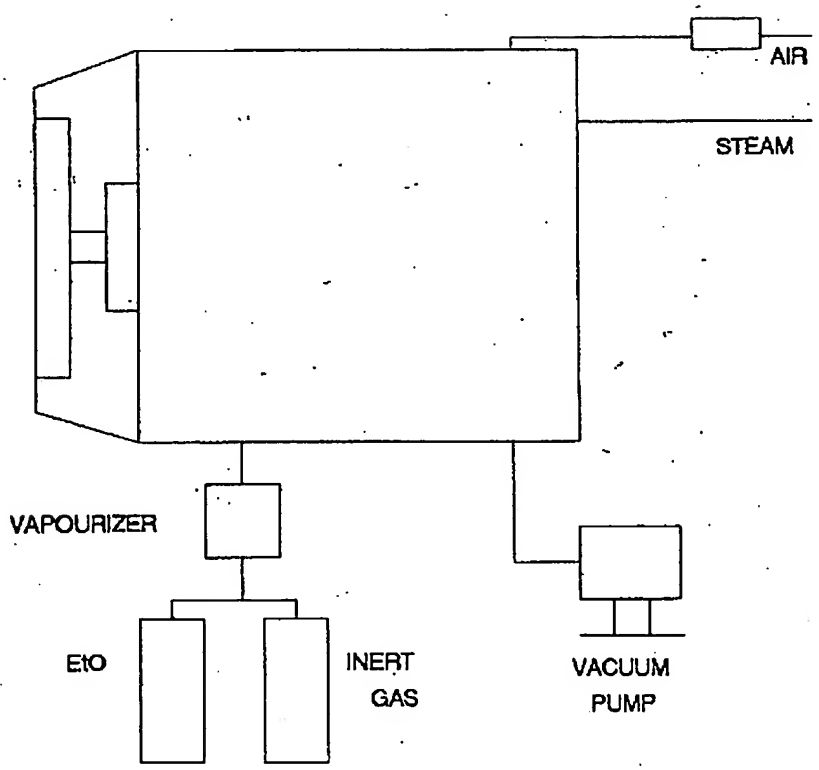

Fig. 2 Schematic representation of a typical ethylene oxide sterilizer.

chamber. There may be associated equipment to monitor gas concentration. All electrical equipment used in association with pure ethylene oxide sterilizers must be sparkproofed.

In some instances there may be an ancillary chamber in which the product load is equilibrated to a specified temperature and humidity prior to its introduction into the sterilizer. The intentions of preconditioning are threefold:

(a) To equilibrate the microorganisms contaminating the product to conditions of temperature and water activity that are optimal for their inactivation by exposure to ethylene oxide.

(b) To equilibrate the packaging (primarily cellulosic materials) to the conditions of the sterilizer in order to prevent deleterious equilibria arising in the sterilization chamber.

(c) To optimize the utilization of the sterilizer. If equilibration is not done elsewhere it must be done in the sterilizer. The residence time of the product in the sterilizer must then be longer than it need be. Preconditioning

chambers that do not operate under pressure are cheaper to build and to operate than sterilizers.

It is critical to ensure that the length of time between the removal of a load from the preconditioning chamber and the beginning of its sterilization cycle is rigorously controlled. It is all too easy, particularly in dry climates with very low humidities, for equilibrium to be rapidly lost.

A typical sterilization cycle (Fig. 3) begins with evacuation of the loaded sterilizer to a predetermined level. It is most important that sufficient vacuum is achieved, not only because it may affect the settings for subsequent phases of the process but also because adequate air removal must be assured to avoid the formation of explosive mixtures with oxygen.

A known amount of steam is then introduced and the sterilizer is left to "soak" for a short period. This is followed by injection of the sterilizing gas to its specified pressure. The sterilizer and its contents are then held under these conditions for the specified time of exposure. At the end of this period the gas is removed by evacuation and replaced by air that has passed through a bacteria-retentive filter.

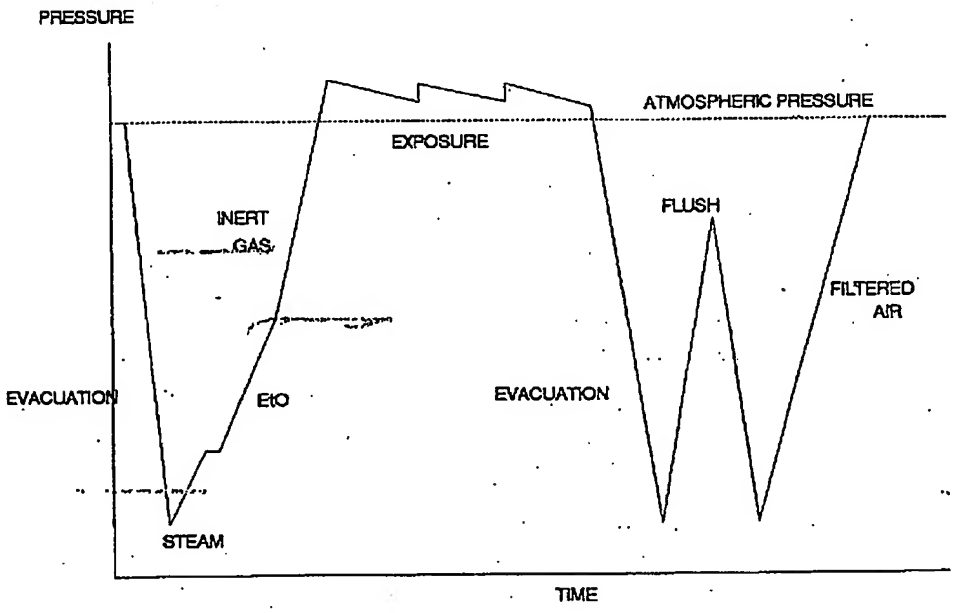

Fig. 3 Typical ethylene oxide sterilization cycle.

In routine sterilization, gas concentrations of 500–800 mg/L, temperatures of 50–60°C, and relative humidities of at least 50% RH are used. The pressure within the sterilizer is important only as it relates to obtaining adequate ethylene oxide concentration as dictated by the gas mixture being used. These operating criteria are as much a function of the technology of the process as they are a reflection of the optimal conditions for sterilization. To a great extent, the gas concentrations, temperatures, and relative humidities used for ethylene oxide sterilization are dictated by the relationships that govern the pressure and temperature of gases at fixed volumes. At temperatures lower than 50°C there may be difficulty in maintaining the vapor state of the gases in the chamber. Higher gas concentrations achieved through increased pressure may result in condensation of water or ethylene oxide unless accompanied by increasing temperature.

The most important phase of the sterilization cycle is the introduction of steam under vacuum. Initial evacuation of the sterilizer is completely unavoidable. It is also potentially deleterious to microbial inactivation. During evacuation the load in the sterilizer loses heat, and more importantly it loses moisture. Steam injection restores the temperature and moisture content of the load to its correct equilibrium. This must be achieved before the sterilant gas is added. There are two main reasons for this:

(a) Ethylene oxide has a greater capacity to penetrate through materials than water has. If the two substances were to be injected into a sterilizer at the same time, the ethylene oxide molecules would permeate and diffuse through the load fastest, leaving the water molecules behind. Ethylene oxide is a comparatively poor sterilant in the absence of moisture.

(b) Water reacts with ethylene oxide. If the two substances were to be injected at the same time, the effective concentration of both systems would be reduced. This would have a deleterious effect on the rate of microbial inactivation.

IV. VALIDATION AND ROUTINE CONTROL OF ETHYLENE OXIDE STERILIZATION

Sterilization by exposure to ethylene oxide is bounded by at least four variables: gas concentration, time of exposure, temperature, and humidity. It is also affected by product design, packaging design, and the composition of packaging materials. The shape, size, and materials of construction of individual sterilizers, the location of gas entry ports, and the presence or absence of forced circulation may all influence sterility assurance. There is no theory to describe these interactions. Validation and routine control of ethylene oxide sterilization processes boils down finally to the integration of all of these variables by reference to biological monitors.

Before validation even, very serious consideration must be given to the nature of the product that is intended to be sterilized and the type of packaging it is to be presented in. Again, it is only experience and experiment that can indicate and confirm the suitability of particular presentations for ethylene oxide sterilization.

Most of the product-related factors need only be evaluated on a broad basis; products compatible with one ethylene oxide sterilization process are generally compatible with most others. Some of the factors that ought to be addressed include

(a) Choice of materials. Although ethylene oxide is probably compatible with a wider range of materials than any other major sterilization process, the choice of materials is not without pitfalls. Some polymers show signs of chemical degradation as a result of chemical reaction during sterilization. Some polymers craze in response to gas mixtures containing fluorinated hydrocarbons but are satisfactory for other ethylene oxide processes. Physical properties may alter, and dimensional tolerances may be changed through shrinkage or expansion. Materials should be chosen to allow degassing (aeration) in a reasonable time frame.

(b) Product design. The product must be designed with the consideration that the sterilant must be able to penetrate to all parts. Functional tolerances should allow for the intense (and often abrupt) pressure and temperature changes that arise in ethylene oxide sterilization.

Consideration of packaging materials should be specific to particular sterilization cycles and should extend beyond primary packaging materials to include the potential effects of secondary packaging (shelf packs or shippers) and pallets on sterility assurance. In some instances these latter factors may need to be addressed on a sterilizer-specific basis, where variations have been suspected of being the cause of erratic and unpredictable biological test failures. The important packaging factors to consider are

(a) Choice of materials. There is a wide variety of materials available for primary packaging (i.e., the packaging that is intended to provide the hermetic environment for the sterilized product) of ethylene oxide sterilizable medical devices. The permeability of the pack to ethylene oxide and water vapor is of utmost importance, but this does not mean that the complete pack has to be made from permeable materials. The pack must be able to withstand pressure changes without materials rupture. This may often lead to composite packs made from permeable and nonpermeable webs; other considerations, for instance price, "printability," and appearance, account for the large number of composite packs currently being sterilized.

Secondary packaging materials are usually made from corrugated cardboard; the grade and the direction of fluting can have serious effects on sterility assurance and on sterility maintenance. Absorption of moisture in secondary packaging may divert the availability of ethylene oxide from its target sites. Insufficient structural rigidity of secondary packaging may lead to damage to primary packaging during or after sterilization with consequent loss of sterility.

(b) Seals. Primary packs must be sealed in a manner that will prevent microbiological ingress, withstand the rigors of the sterilization cycle, and still be easily openable by the customer at point of use. Within some packs there may be more than one type of seal, some intended to be opened, others intended to be permanently closed. Syringe packs usually direct the user to the openable seal by a printed instruction. Often this is disregarded in clinical practice, where users have found it easier to burst the packets open. The characteristics of good microbiological seals and of equipment that is capable of producing consistent seal quality can only be evaluated empirically.

A. Validation of Ethylene Oxide Sterilization Processes

The overall scheme of validation of ethylene oxide sterilization is no different from validation of any other process. With new equipment it requires careful consideration of design before specification (Design Qualification), confirmation that received equipment conforms to its specification (Installation Qualification), and confirmation that received equipment can perform its specified functions when assembled, plumbed in, and linked up to local services (Operational Qualification).

Process qualification of ethylene oxide sterilization is both sterilizer specific and product specific. It is particularly directed toward the measurable parameters of the whole sterilization cycle. If external preconditioning is used, validation should address the measurable parameters of all combinations of preconditioning chamber and sterilizer. Where one preconditioning chamber may serve two or more sterilizers, or where one sterilizer may be served by two or more preconditioning chambers, cycle-to-cycle variability should be minimal. The essence of successful ethylene oxide sterilization lies in the establishment of a complete process specification with very tight tolerances. The integral effects of the specified conditions on assurance of sterility can only be validated by reference to biological monitors.

1. Load Specification: The product and its primary and secondary packaging must be specified. The loading pattern of primary packs into shelf packs should be specified. Occlusion of gas-permeable surfaces one against the other should be avoided if sterility is to be assured.

The loading pattern of shelf packs on pallets must also be specified. Patterns that allow good circulation of gas to all parts of the load, designed with free space and "chimneys," are best from a sterilization standpoint but may conflict with commercial considerations. Sterility assurance, cycle duration, sterilizer capacity, and throughput rates are inextricably linked to validated loading patterns for ethylene oxide sterilization. A further factor involved in determining loading patterns is the rigors of ethylene oxide sterilization, which can affect the strength of corrugated cardboard. Partial or total collapse of a stacked pallet may involve some compromise of sterility. The use of "dividers" to give greater structural support to stacked pallets may impede gas penetration. All of these factors can only be addressed empirically; any significant change to a successful loading pattern must be validated thoroughly.

If more than one product is to be sterilized at the same time in the same sterilizer, process validation should be completed for each combination. The lot size in many manufacturing operations is "tailored" to sterilizer capacity, and in such instances it should not be difficult to avoid mixed loads. This may be more difficult for contract sterilization operations. Ethylene oxide sterilization contracts should address the validation of mixed loads or prohibit them. Both routes have cost implications.

The types of pallets should be specified—wood, aluminum, or some other material. Ethylene oxide is not absorbed by metal pallets, but the same cannot be said for wood. Wood is commonly used but difficult to control. Hard woods may absorb differently from soft woods, and some pallets may be water saturated, while others may be quite dry. Some of the unexpected and unpredictable sterilization failures seen in ethylene oxide sterilization may be associated with use of wood pallets. Once validated, change from one type of material to another should not be permitted.

2. *Equipment Specification*: Any change in process equipment or any introduction of new process equipment should be considered for validation. Biological validation may not always be necessary if there is sufficient physical or chemical evidence to demonstrate equivalence. All equipment should be identified; specifications, drawings, and instruction and maintenance manuals should be obtained and referenced in validation documentation. No list of equipment requiring validation can profess to be comprehensive. All functional equipment should be subject to scheduled inspection and preventative maintenance programs. All measuring devices must be calibrated and scheduled for regular recalibration.

a. External Preconditioning Chambers. External preconditioning chambers are not required to be as elaborate as sterilizers. This may in some cases lead to the belief that they are of only minor significance to the assurance of sterility. This is not correct. Due care and attention must be given to the design and specification of external preconditioning chambers.

They may be built to hold more than one sterilizer load, but if all loads are not to be removed at the same time some alarm or device should control the length of time that access doors are left open. This should be minimal. Preconditioning chambers should be of sufficient size to allow free circulation of air and moisture to all parts of the loads. The criteria for temperature and humidity specified for preconditioning rooms should be identical or very close to those obtaining in the sterilizer; in practice that means something close to those found in a sauna but less pleasant. The finish of preconditioning rooms should be robust enough to tolerate these conditions. Forced air circulation is necessary to the attainment of uniform conditions; fans should be equipped with alarms to indicate any failure.

Temperature and humidity in the preconditioning chamber should be specified and continuously monitored and recorded. These criteria should be related to the temperature and humidity obtained within the load. The object of preconditioning is to equilibrate the load to the conditions of the sterilizer; sufficient holding time in the preconditioning chamber should be specified to allow this to happen.

A maximum time limit between removal of a load from the preconditioning chamber and the commencement of sterilization should be specified. This may be particularly important in low-humidity locations.

b. Sterilizers and Ancillary Equipment. Allowing for all the normal criteria that apply to pressure vessels used for sterilization, the most important considerations to be specified for ethylene oxide sterilizers are the devices that contribute to the reproducibility and uniformity of control. Forced circulation may be necessary, and any such devices, as in the case of preconditioning chambers, should be specified to have alarms to indicate failure.

Gas concentration must be specified and demonstrated to be achieved. There are three methods for control and monitoring available. There are direct methods involving infrared analysis or gas chromatography. However, indirect methods are more robust and for that reason ought to be specified either on their own or alongside direct methods. Use of a sensitive, vulnerable, direct method of gas concentation without indirect backup in large-scale ethylene oxide sterilizers is usually seen to be an unacceptable commercial risk.

The most commonly used indirect method is by measurement of differential pressure within the sterilizer by means of pressure recorders. This method is permissible and valid only when using gas sources that are certified by the supplier, as it depends totally upon the differential pressure arising from ethylene oxide and not from some other gas. The gas concentration can be related to pressure and temperature through the formula

$$c = \frac{K \times MW \times P}{T}$$

where c = gas concentration (mg/L); MW = the molecular weight of the gas (MW of ethylene oxide = 44); K = a constant, 732.2; P = the increase in pressure in inches of Hg; and T = temperature in °Rankeine (460 + °F).

The second indirect method is by measurement of the weight of ethylene oxide delivered from the feed containers to the sterilizer. This method assumes no leakage, liquefaction, or polymerization of ethylene oxide in the gas lines connecting the gas source to the sterilizer. It is recommended that the two indirect methods be used in conjunction with each other. The weight loss method ensures that the increase in pressure is in fact due to gas from the ethylene oxide feed container and not from diluent gas or some other source; whereas the pressure method provides an ongoing index of gas concentration during the exposure period. Gas makeups should be automated and specified to be drawn from the ethylene oxide feed tanks, not from the diluent gas. Gas makeup may be controlled by pressure switches or by pressure transducers connected to solenoid valves controlling gas flow.

Direct methods of measuring gas concentration include gas chromatography and infrared spectroscopy. Both methods are dependent upon small samples, and the problems of drawing these samples should not be underestimated. The location of multiple sample ports should be such that a representative sample of a hopefully homogeneous gas mixture is obtainable. With most sterilizers operating at positive pressures, it is not usually necessary to have any special means of withdrawing the gas, but it is essential to have sample lines heated and insulated to avoid condensation of gas and water between the sterilizer and the analytical instrument.

Both gas chromatography and infrared analysis are dependent upon the instrumentation being calibrated against certified ethylene oxide supplies. Gas chromatography results are obtained as mol %, values which must then be converted to specifications defined in mg/L. Infrared results are directly correlated to mg/L.

Chamber temperature should be controllable and monitored throughout all cycles. The temperature obtained in a load is a function of the initial product temperature and its specific heat, the amount of steam injected, and the effectiveness of the insulation or the jacket at preventing heat loss. Temperature during the exposure phase of ethylene oxide sterilization cycles is not controlled by steam injection into the chamber as occurs in thermal sterilization. Loss of temperature may be compensated for by steam injection into the jacket. The control probe is usually located within the chamber rather than within the jacket, and control of temperature is a good deal less fine than in steam sterilizers because of the slower response through the jacket. Ethylene oxide sterilizers should be equipped with both jacket and chamber temperature indicators, and with chamber temperature recorders. Sterilizers should be specified with access

ports to allow chamber and load temperature profiles to be obtained for the purposes of process validation.

Measurement of the humidity in the chamber and in the load has the least satisfactory technology of all the critical parameters of ethylene oxide sterilization. Direct measurement with gas chromatography or infrared analysis may not be reliable in the presence of ethylene oxide. Specification of the pressure increase obtained from steam injection is normally thought to be a satisfactory means of controlling humidity, but it does not offer a monitoring option.

The time of exposure may be manually or automatically controlled. Other time factors must also be specified and alarmed because they may affect sterility assurance in an unpredictable fashion or they may be indicative of other process problems. These time factors include the rate of evacuation at the beginning and at the end of the cycle, and the rate of increase of pressure as a result of gas injection.

For air ingress at the end of the cycle, ethylene oxide sterilizers should be equipped with sterilizing filters. Although the primary packaging material ought to have been chosen to be a barrier to microbial ingress, there remains the possibility that the significant pressure differentials and air flow rates that are obtained at the end of sterilization may be beyond validated tolerances.

The condition of the gas vaporizer is a further important consideration to ethylene oxide sterilization. All cylinder supplies of ethylene oxide present the gas in liquid form under pressure, which must then be vaporized before admission to the sterilizer. Inadequate temperatures in vaporizers may lead to the introduction of liquid ethylene oxide into the sterilizer. This is undesirable because it will not fulfill its purpose and because of staining and damage to product and packaging. Overly high temperatures may lead to degradation of the ethylene oxide with resultant polymer buildup restricting gas flow in the feed lines.

3. Process Validation (Physical): The equipment and the proposed preconditioning and operating cycles must be carefully specified in detail and with tight tolerances before starting process validation studies.

Multiprobe temperature and humidity distribution profiles should be obtained for empty preconditioning chambers, and temperature penetration profiles should be obtained with probes located within loads. The purpose of these studies is to demonstrate that the load is being uniformly equilibrated to the temperature (and by inference to the humidity) of the sterilizer within the proposed preconditioning time frame. Any serious lack of uniformity detected during validation studies should be investigated and corrected (even if only by extending the time of the preconditioning cycle).

It is normal practice to run large preconditioning chambers under operational conditions at all times irrespective of whether they are in use or not. If it

is intended to use them on an ad hoc basis, validation studies should also cover the time taken for the chamber and the load to attain specified operating conditions.

The sterilizer and its associated pipework should be tested to ensure that it is adequate to maintain the positive pressures and vacuum pressures proposed in the cycle specification. The main thrust of physical validation is through temperature profiles.

Replicate temperature distribution profiles (from 3 to 24 sensors per cycle according to the size of the sterilizer) should be obtained for empty sterilizers operated to the proposed cycle specification. All parameters should be within their specified tolerances throughout validation cycles. For economic reasons an inert gas may be substituted for ethylene oxide in these studies. The *AAMI Guideline for Industrial Ethylene Oxide Sterilization of Medical Devices* [6] allows a variation of ± 3°C about the nominal specified temperature; sterilizer manufacturers [7] claim ± 2°C to be possible, this being a function of the types of controller used and of jacket design. At least one empty chamber temperature distribution profile should be run using ethylene oxide to discern whether there are any significant changes when the sterilant is being injected. Problems with vaporizers may be revealed by this means.

Empty chamber studies are sterilizer specific. Further process validation work is product specific (load specific) and may be done with dummy product if required. If this option is exercised, care must be taken to ensure that dummy loads are truly representative of genuine product. Scrap product is ideal for this purpose but may not be readily available for high cost products (e.g., cardiac pacemakers). If good product is used in validation, it should not be released as sterile until the validation program has been completed and signed off as satisfactory.

Load configurations and packaging materials have a significant effect on the rate of heat transfer into the product. Since it is microorganisms within the product that are to be inactivated, it is to the product that the critical process conditions must be delivered. Multiprobe temperature penetration profiles over replicate cycles are necessary. A wider tolerance of ± 5°C can be expected [6] due to slower response times. Cold spots (if any) should be identified and corrected, or specifically examined in the biological phase of process validation.

4. Process Validation (Biological): Biological validation is the most critical element of process validation of ethylene oxide sterilization. It is the only method of integrating the interaction of gas concentration, humidity, temperature, time, sterilizer effects, load effects, etc. It must demonstrate that the SAL being obtained is no worse than 10^{-6}, and it must demonstrate uniformity of treatment and it must provide the basis for routine monitoring. It is the only guarantee that the specifications for product and for process achieve sterility. Some preliminary work done in laboratory-scale sterilizers may provide favor-

able indications, but in the end trials must be done with actual product in a production-scale sterilizer.

The microorganisms used for biological validation of ethylene oxide sterilization are the spores of *Bacillus subtilis* var *niger (Bacillus globigii)*. These spores are quite resistant to ethylene oxide though not the most resistant known. They are indicator organisms. The spores are stable over time and ranges of storage temperatures, and they are easily recognizable in culture because their growth has an orange pellicle. However, exactly what constitutes a satisfactory biological monitor using these spores and what constitutes an unsatisfactory biological monitor continues to be a subject of debate.

The topic of biological validation of ethylene oxide sterilization processes can be subdivided under two headings, microbiological monitor systems and process challenge systems.

a. Microbiological Monitor Systems. The most contentious issue surrounding the use of biological monitors for validation and routine control of ethylene oxide sterilization is that criteria for standardization have never been described sufficiently well for there to have been international acceptance in the manner that physical and chemical standards have been accepted. Standardization has been attempted by various organizations, for instance the USP and the U.K. Department of Health.

All attempts at standardization have agreed that certain general characteristics of biological monitors should be specified; these are to use a recognized strain of microorganism, to specify the number of microorganisms per monitor, to specify a *D*-value, and to specify an expiry date.

Only the first of these characteristics (use of spores of *B. subtilis* var *niger* ATCC 9372 or NCTC 10073) is without some form of complication with regard to ethylene oxide monitors.

Even the standardization of numbers of spores per monitor is not straightforward. The numbers of spores recovered from monitors is not likely to correspond to the numbers inoculated. The choice of carrier, the method of loading the spores onto the carrier, and the methods of spore removal and recovery may influence differences from the specified number. For instance, because of the fibrous nature of papers, it is easier to remove spores from aluminum carriers than from paper carriers. This does not necessarily mean that aluminum carriers are better than paper carriers for the purposes of monitoring sterilization cycles. Other variables related to adherence include "wettability" and the speed and manner in which a spore suspension spreads across the surfaces of a carrier, perhaps spreading evenly, perhaps forming clumps. This makes it difficult to translate a specified number of spores per carrier into a process for preparing consistent biological monitors.

Commercially available spore strips are usually intended to have 10^6 viable recoverable spores per strip. They may be loaded onto carriers by indi-

vidual inoculation or by running a carrier strip through a bath of spore suspension at a controlled rate.

The response of particular microorganisms to particular sterilization processes is usually expressed through the *D*-value. However, the *D*-value of spores used to monitor ethylene oxide sterilization processes is of less relevance to practical sterilization than *D*-values of microorganisms versus other sterilization processes. If biological monitors were to be used in conjunction with gamma radiation sterilization (noting that this is not necessary), the D_{10}-value versus the single parameter of absorbed dose would be directly relatable across all cobalt-60 gamma irradiators. D_T values for thermal sterilization processes are transferrable from one autoclave, oven, or tunnel to another. With ethylene oxide this is not the case; the *D*-value of a spore population is relevant only to the conditions of gas concentration, temperature, humidity, time of exposure, and gassing up and degassing times for which it was determined.

Attempts have been made to standardize at least the conditions in which *D*-values may be determined, AAMI [8] have specified a sterilizing vessel, termed a biological indicator evaluator resistometer (BIER vessel), which allows rapid attainment and termination of exposure conditions in a precise and accurate manner.

The time to reach target gas concentration must be less than 60 s, and gas concentration is specified as 600 mg/L ± 30 mg/L at 54°C ± 1°C and 50 to 70% RH. The time to exhaust a BIER vessel must be less than 60 s and accurate to ± 10 s. It would be an unusual production sterilizer that could conform to these criteria.

In addition to these fundamental problems of translating ethylene oxide *D*-values from one situation to another, the *D*-value obtained even in the best-controlled BIER vessel may be affected quite significantly by the methods used to prepare the monitors and the methods used to determine resistance.

Most significantly, biological monitors prepared at different levels of dryness do not respond in the same manner to ethylene oxide inactivation.

In other words, the *D*-value is a function of the previous history of the monitor as well as of the sterilizer in which it was determined. The composition of the fluid from which the spores were dried may also influence *D*-values by coating the spores with a layer of material through which moisture or ethylene oxide may have restricted permeability. This also gives importance to the conditions in which the spores were grown (complex or defined media) and washed. Graham [10] quotes *D*-values of 2.4 min and 3.5 min for the same strain of *B. subtilis* var *niger* grown in different liquid media and exposed to ethylene oxide under identical conditions.

Finally, the requirement to specify an expiry date implies that something is going to deteriorate or change over time. The most obvious characteristics are numbers of spores per monitor (do the spores die over time? do they lose adher-

ence to the carrier over time?) and *D*-values. Stability over time can only be determined empirically; again, it is likely to be a function of the biological monitor itself and of the method of preparation of the biological monitor.

b. Process Challenge Systems. Broadly there are three methods by which microbiological monitor organisms may be presented as process challenges. These are

(a) Inoculated carriers. These are generally in the form of spore strips; strips of paper or aluminum inoculated with spores of *B. subtilis* var *niger*. Commercially available spore strips are usually individually packed in glassine envelopes.

(b) Self-contained biological monitors. These are sophisticated variants of inoculated carriers in which the recovery medium is an integral part of the monitor. For ethylene oxide the spores are mounted on a carrier that is in one compartment of a two-compartment unit. In the other compartment is the recovery medium. After exposure, the seal between the two compartments is broken open and the surviving spores (if any) are incubated in the medium.

(c) Inoculated products. A very small proportion of the total number of biological monitors used to challenge ethylene oxide sterilization processes will be actual product samples carrying an inoculum of spores. Theoretically this is the most valuable indicator of sterility assurance. In most cases it loses out to practicality. Many medical products are too bulky to incubate *in situ*, and even if this were overcome the amount of medium and incubator space required to cater for large numbers of biological monitors of this type might soon become prohibitive. Removal of spores from the inoculated device into some other carrier for incubation introduces a further variable and increases the complexity of laboratory manipulations.

Of the three types of carrier, the spore strip is the most commonly used. Once this choice is made there are several other essential decisions.

The first of these is where to place the microbiological monitor in the product. The ruling is that it should be placed in the location most difficult to sterilize. To some extent this is a reflection of professional judgement. It is a curious anomaly that most ethylene oxide sterilizers of hypodermic products judge the most difficult position within the product to be between the two "lands" or "ribs" of the plunger tip because this is an enclosed cavity. However, at the same time, it is also the location where ethylene oxide is most likely to persist longest because of its preferential absorption into rubber. The location most difficult to sterilize may not be amenable to placement of biological monitors. In these circumstances it is usually recommended to use some other product or device packed in a similar or identical manner to simulate the actual product.

The number of spores per strip and the number of strips per load should for validation purposes be related in some way to the bioburden of the product. What type of relationship this should be is less obvious. There are two broad approaches to this; the first is to relate the microbiological challenge on each spore strip to the average bioburden on individual products and the required level of sterility assurance (SAL); the second is to relate the total microbiological challenge in the sterilizer load to the total bioburden within the sterilizer.

Both approaches require some estimation of product bioburden. It is not advisable for ethylene oxide sterilization processes to be validated without at least some estimates of numbers of product contaminants. This is irrespective of whether cycle development is by the so-called overkill or the so-called bioburden method (see below).

If the number of spores per load is to be related to the total bioburden of the load, the average bioburden per item must be multiplied by the number of items in the load to give an estimate of the total bioburden in the load. The number of spore strips to be used in validation may be calculated by dividing this number by the number of spores per biological monitor thus

$$\text{Number of spore strips per load} = N_0 \times \frac{m}{C}$$

where N_0 = the average number of contaminants per item prior to sterilization, m = the number of items per load, and C = the number of spores per biological monitor.

If the number of spores per spore strip and the number of spores per validation load is to be related to the individual product item and a sterility assurance level of 10^{-6}, it is first necessary to know the average number of contaminants per product item. In the interests of conservatism this number may be rounded up or supplemented by a safety factor. The target is to use as many spore strips as is necessary to provide assurance that this bioburden is being inactivated to an SAL of 10^{-6}. This can be calculated from

$$\text{Number of spores per load} = N_0 + \frac{1}{\text{SAL}}$$

where N_0 = the average number of contaminants per item prior to sterilization. and SAL = the required sterility assurance level.

The number of spore strips per load can be obtained by dividing this figure by the number of spores per strip.

Given that these methods can provide a means of deciding how many biological monitors should be used for validation purposes, there are two approaches to cycle validation. These have been termed overkill and bioburden.

An overkill cycle is quite simply one that inactivates the microbiological challenge plus an additional safety factor. As a rule of thumb, the shortest expo-

sure time obtained in validation runs that will consistently inactivate all of the microbiological challenge organisms should be doubled to specify an adequate overkill cycle.

Bioburden cycles normally require resistance data as well as estimates of numbers of microbial contaminants. In this respect AAMI are using the term bioburden in its broadest sense, almost as a synonym for microflora.

Resistance work cannot be done in large-scale production sterilizers, because the gassing and degassing times are too long. These must be done in laboratory-scale equipment or BIER vessels. They should be done preferably for microorganisms actually isolated from the product and with microbiological monitors. A comparison should be made of the resistance (D-values) of both types of microorganism in simple situations (say on strips held in glass petri dishes) and in product items or simulated product items. The cycle should be chosen on the basis of the determined resistance of the bioburden being sufficiently treated within the specified parameters to provide a 10^{-6} SAL. Final proof of this must be obtained with microbiological monitors in the production sterilizer. As an example, assuming that the average bioburden per item is equal to n microorganisms of D-value D_b, the exposure time for a 10^{-6} SAL may be calculated from

$$\text{Exposure time} = D_b \cdot (\log n + 6)$$

The number of spores per biological monitor required to be inactivated to verify that this cycle is effective can then be calculated from

$$\text{Log number of spores per monitor} = D_b \cdot \frac{(\log n + 6)}{D_m}$$

where D_m = D-value of *Bacillus subtilis* var *niger*.

For validation purposes, microbiological monitors are intended not only to provide an index of achievement of SAL, but also to provide (among other things) some index of process uniformity. They must therefore be placed throughout the load in pallet positions close to and far from the entry ports for gas and steam, near the surfaces and deep within stacked pallets. Microbiological monitors should be placed alongside temperature sensors during validation, but it should be noted that the sensors may introduce a route for easier access of gas than might occur in their absence. The choice of locations for biological monitors is in the long run arbitrary.

B. Routine Control of Ethylene Oxide Sterilization

The emphasis for routine control of irradiation sterilization and thermal sterilization has been toward tight control of the physical parameters that lead to microbial inactivation rather than toward control through biological testing. At one time there would have been an emphasis on biological methods for controlling

these other sterilization processes, but as the scientific basis of these processes has become better known, and their technology has become better controlled, biological monitoring has diminished in importance. This is not yet the case with ethylene oxide sterilization. Both biological and physical methods of monitoring are absolutely necessary to provide reasonable assurance of sterility.

The first requirement of a routine monitoring program for ethylene oxide sterilization is specification of the critical parameters. Any excursion beyond the specified tolerances for any one of these critical parameters must stimulate rejection or resterilization irrespective of whether biological monitoring criteria are met. This acknowledges the fallibility of biological monitoring methods and the limitations on the numbers of biological monitors that may be used practically. The instrumentation used to monitor these characteristics must be independent of the instrumentation used for control.

Other excursions beyond less critical specifications and tolerances should be noted as a matter of routine in the event of these providing an early warning of some progressive deterioration or loss of control that may in the long run impact upon sterility or safety, for instance wear and tear on vacuum pumps.

The second critical requirement for routine monitoring is a biological monitoring system. Biological monitors should be placed in the product load, retrieved promptly after sterilization finishes, be left for a controlled period to lose any residues or traces of ethylene oxide, and then cultivated in appropriate recovery media.

Fewer biological monitors are needed for routine monitoring than would be used for validation. There should be some concentration on cold spots (if any), but at the same time there should be some attempt at random or representative covering of all parts of the sterilizer and of the load. The history and reproducibility of particular ethylene oxide sterilization technologies may influence the confidence that can be placed on a particular process. Precise and reproducible technology does not merit as much biological monitoring as less reliable equipment. A sound sterilization history of a particular sterilizer coupled with a particular cycle and a particular product does not require as much biological monitoring as a new sterilizer, new product, or new cycle. How many biological monitors is a matter of professional judgement.

Most biological monitoring is done on a quantal response (growth/no growth) basis, and if any one biological monitor shows growth the load should be rejected or resterilized. Once again this decision should be made independently and irrespective of whether physical process specifications have been met. This acknowledges the empiricism of the ethylene oxide sterilization process. With so many variables it can be quite possible to fail to achieve sterilizing conditions at some point or points locally in the load. If there is biological evidence of this having happened the decision can only be the conservative one.

Spores of *B. subtilis* var *niger* form an orange pellicle in simple standard recovery media, so failure is easy to recognize and simple to distinguish from incidental contamination. Laboratories with high incidences of incidental contamination should seriously review their procedures for recovering biological monitors from the sterilizer and from the product. They should also review their aseptic techniques. This emphasis acknowledges that microorganisms compete for nutrients such that faster growing contaminants may obscure survival of the biological monitor.

One of the major commercial difficulties with biological monitoring is the incubation of the biological monitors. Various sources may recommend 7, 10, or 14 days. With reliable technology and a satisfactory sterilization history it is quite reasonable to divorce the incubation of biological monitors from the shipment of product from the sterilization site, as long as the product is not actually put into use and is accountable and retrievable in the event of a subsequent biological failure. This is not parametric release, but a commercial risk, and it should be exercised with considerable care and only when processes subsequent to sterilization but concurrent with incubation, e.g., degassing, packing, and labelling in shippers, transportation, and warehousing, operate over a time scale that ensures that nonsterile product is unlikely to reach the final user before completion of incubation.

In addition to the use of biological monitors it is also advisable with ethylene oxide sterilization processes to include a routine batch-by-batch pharmacopoeial sterility test. Its statistical limitations remain as a barrier to its value for confirming sterility. However, it should not be discounted as a further means of investigating the possibility of failure to achieve sterility (i.e., as a test for nonsterility) in a poorly predictable situation.

V. HEALTH AND SAFETY

Ethylene oxide damages biological systems. Its effects are not peculiar to microorganisms, but apply to all biological systems. Ethylene oxide and its by-products are toxic, mutagenic, and carcinogenic to animals and humans. Ideally ethylene oxide residues should not be present on medical products. In practice there are technologies available to ensure that the use of ethylene oxide need not result in an unacceptably high risk to human health.

Acute effects of ethylene oxide and its by-product ethylene chlorhydrin (CH_2ClCH_2OH), formed by reaction with chloride ions, include symptoms of nausea, dizziness, and signs of mental disturbance. Ethylene chlorhydrin may also cause kidney and liver degeneration. The most serious effects of both substances may lead to cancer. Exposure to ethylene oxide induces irreversible chromosomal aberrations (sister chromatid exchange) and other precancerous changes in the peripheral lymphocytes.

There are two broad groups at risk. The first of these comprises ethylene oxide sterilization workers who are subject to exposure by inhalation and perhaps to skin contact with liquid ethylene oxide while changing gas cylinders. The second group comprises the recipients of ethylene oxide sterilized products, including patients who may be receiving treatment and medical or nursing staff who must come into regular and frequent contact with ethylene oxide sterilized products.

The group at highest risk are sterilization workers, patients on hemodyalysis equipment, and persistent users of hypodermic equipment (e.g., diabetics using insulin syringes) and habitual users of ethylene oxide sterilized gloves. There is a middle risk category of patients on intravenous therapy using ethylene oxide sterilized infusion sets over a comparatively short period of time. In numbers this is the largest group. The lowest risk is to patients who receive one time implants (e.g., cardiac pacemakers), one single dose of ethylene oxide absorbed completely.

The most stringent attitudes to worker protection have been those of the Occupational Safety and Health Administration in the U.S.A. There are three limit standards to be considered. The permissible exposure limit (PEL) is a measure of good industrial hygiene practice expressed as an 8-h time weighted average (TWA8). The PEL set by OSHA is 1 ppm TWA8 measured in a manner representative of the employees' breathing zone. Personnel are subject to medical surveillance; areas where greater ethylene oxide exposure may be expected must be identified, respiratory protection must be provided for particular tasks, and risks should be identified through appropriate signs and labels. If an action limit of 0.5 ppm TWA8 is being consistently achieved, then the frequency of medical surveillance and monitoring may be reduced. The third limit is an excursion limit (EL) not to be exceeded over a 15-min period. This has been set at 5 ppm.

In Europe PELs for ethylene oxide range from 1 ppm TWA8 in Belgium and Denmark through 5 ppm TWA8 in the U.K. and France up to 50 ppm TWA8 in the Netherlands. France has a 15-min EL of 10 ppm.

Surrounding these limits are a series of complications. In general PELs can be attained by use of segregated areas for ethylene oxide sterilization and ethylene oxide storage. Ventilation is of utmost importance, and, since ethylene oxide is heavier than air, low-level exhaust systems are to be preferred. Other engineering measures may include interlocks and remote control consoles. Short-term excursion limits (ELs) may necessitate positive pressure self-contained respiratory protection to be used for particular tasks, for instance unloading sterilizers and changing gas cylinders. Personal protection should not, however, be considered until it can be shown conclusively that ELs cannot be achieved by engineering controls or changed workplace practices.

Ethylene oxide residues remaining on products present a more complicated picture. Limits should properly be based on risk assessment. Satisfactory risk

assessment involves an analysis of a multitude of complex factors concerning particular medical products, their frequency of usage, and the characteristics of the recipients. Some still unfinalized residue limits provided by the FDA in 1978 provide a guideline to appropriate targets. These range from 5 to 250 ppm by weight of device depending on the type of device [11]. By and large these recommendations follow the risk categories described previously. There is some conjecture over ppm by weight of device being the most appropriate measure to define limits. In many cases surface area in contact with the recipient's tissue or in contact with fluids being infused may be argued to be more appropriate.

Methods of extraction and analysis have been published by the Association for the Advancement of Medical Instrumentation [12]. Water or other aqueous systems are most commonly used for extraction. Two extraction methods are recommended, exhaustive extraction and simulated use. In fact both methods, if used correctly, represent simulated use. Exhaustive extraction is recommended for devices such as implants, which by merit of their prolonged contact with tissue over time can be expected to transfer all of their residual ethylene oxide to the recipient. Simulated use extraction of a less exhaustive nature might include fluid path extraction over a simulated maximum hold period for infusion sets and hypodermic syringes. Analysis is by gas chromatography.

There are four ways in which ethylene oxide may be retained in products at the end of sterilization cycles. These are as gaseous ethylene oxide, as ethylene oxide dissolved in water, as ethylene oxide within but not attached to the product or packaging material, and as molecularly adsorbed or absorbed ethylene oxide [13]. The total amount of residual ethylene oxide and the balance among the four forms of residue at the end of sterilization are functions of the sterilization process conditions, the composition of the product, the size of the product, the packaging materials, and the packing density. Dissipation of residues after sterilization is a function of the product- and packaging-related factors listed above plus the conditions in which the product is being held (aeration).

The amount of residual ethylene oxide in a product can be significantly influenced by sterilization process conditions. Gas concentrations and exposure times within the exposure period of the cycle should be sufficient to achieve sterility, but their effects on residues should be considered before prolonging them unnecessarily. Importantly, free gaseous ethylene oxide is easiest to remove from product loads, and this is best addressed by postexposure evacuation and aeration. Multiple evacuations and forced-circulation aeration at temperatures around 30°C have been found to be effective. The effects of increased temperatures extend beyond the removal of the free gas to the removal of other forms of bound ethylene oxide.

After removal of the load from the sterilizer, further dissipation of residues is a function of time, temperature, and ventilation. Generally, the rate of ethylene oxide dissipation doubles for every 10°C rise in temperature (the Q_{10} is

equal to 2), and ventilation should be sufficient to maintain a concentration gradient between the ethylene oxide in the product and the ethylene oxide in the atmosphere. Movement of ethylene oxide from the product into the atmosphere is governed by Fick's laws of diffusion. Given that there are technological and commercial restrictions on the conditions in which ethylene oxide sterilized products can be held after sterilization and before release to the market, serious consideration should be given to the ways in which product and packaging composition and design can affect the dissipation of ethylene oxide.

It is paradoxical that the abilities of ethylene oxide to penetrate materials that make it an effective sterilant are the same abilities that create residues. Polymeric materials are very permeable to ethylene oxide. Permeability is affected by the solubility of the gas in the polymer and the diffusivity of the polymer to ethylene oxide. Ethylene oxide is less soluble in polyethylene and polyesters (around 10,000 ppm) than in say cellulosics or PVC (around 30,000 to 40,000 ppm according to the level of plasticizers present in the formulation); soft plastics and natural rubbers have higher diffusion coefficients for ethylene oxide than harder polymers such as acrylics and styrenes [14]. Polymers with high diffusion coefficients will reach saturation solubility quicker than those with lower diffusion coefficients. A polymer that takes up residues only slowly will release them only slowly. Since devices may often be manufactured with several different types of polymeric material, it is difficult to predict or quantify overall residue levels and practical rates of dissipation. A component such as the rubber plunger tip may as a result of its high diffusivity and thickness amount for most of the residues in a hypodermic syringe, although it is in itself only a minor component.

Much of what has been said about the movement of ethylene oxide in and out of products also applies to packaging materials. Primary packaging materials are only very rarely of a significant thickness, and should be chosen to allow rapid penetration of ethylene oxide to the product during the exposure period of the sterilization cycle. They should therefore present an insignificant barrier to the dissipation of residues. Molecules released from the product dissolve in the permeable primary packaging materials on the side with the higher concentration and diffuse in the direction of the concentration gradient toward the side with the lower concentration of ethylene oxide. The residues desorb to the atmosphere on the side of lower concentration.

In the long run, corrugated cardboard boxes and wooden pallets may allow residues to hang around the load and the product longer than necessary. Loads should not be left to aerate in conditions where ventilation may be restricted by too great packing densities or where some pallets may occlude air movement around others.

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Transport of Ethylene Oxide Through Polymer Films

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Synopsis

The transport of gaseous ethylene oxide (EtO) in several polymer films is studied using the carrier gas method of measurement. Permeability, solubility, and diffusion coefficients describing ethylene oxide (EtO) transport in polypropylene, polyvinylchloride, Teflon-FEP copolymer, and polyethylene films have been obtained over a 30 Celsius degree range at a low concentration of EtO using the carrier gas method of measurement. The results indicate that the diffusion of EtO in polyethylene is independent of penetrant concentration over the range of concentrations used. However, concentration-independent diffusion could not be verified directly for the other films studied. Two different techniques of determining diffusion coefficients were used, and within the precision of the data both yield the same result. An excess enthalpy of solution for the solubility of EtO in Teflon-FEP copolymer was calculated, an observation that suggests that dual-mode sorption may be taking place.

INTRODUCTION

In the medical products industry, ethylene oxide (EtO) is widely used as a gaseous sterilant.[1] However, since many of these products are frequently used well after sterilization, the need for packaging materials which maintain the sterility of the articles virtually indefinitely is quite apparent. Polymeric films such as those made of polyethylene and polyvinylchloride, or these plastics in combination with traditional packaging materials like kraft paper have proven quite successful in this regard.

Articles being treated invariably absorb some of the sterilant which has been shown recently to be a toxic substance.[2] Thus, while it is important that the sterility of the article be maintained, it is equally important that the ethylene oxide residues be allowed to dissipate from the sealed package. The package may, for example, be stored under ambient conditions for a considerable length of time or it may be degassed under vacuum. Hence, not only must the packaging film used act as a microbial barrier, it must also be sufficiently penetrable to EtO so that evacuation of the sterilant may take place within a reasonable period of time. How long a package must be stored before residual concentrations reach permissible levels will be determined by the solubility and diffusivity of the sterilant in the polymer.[3]

The present investigation is a continuation of work in our laboratory on the transport of gases through various polymer films.[4-8] The chief aim of the

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work reported in this paper is to characterize the transport of ethylene oxide in some typical polymeric films. To that end, we have constructed in our laboratory an apparatus based on the carrier gas method of measurement,[9-20] and have obtained permeability, solubility, and diffusion coefficients for several ethylene oxide/polymer pairs over a wide temperature range. Data such as these should be useful in recommending suitable packaging materials as well as in providing an overview of the nature of ethylene oxide transport in these polymers.

THEORETICAL PRINCIPLES

The diffusion of gases or vapors in polymer films can be adequately described by Fick's first law with a concentration-independent diffusion coefficient if there is no interaction between the polymer and diffusate.[21] Thus,

$$J/A = -D(dC/dx) \tag{1}$$

where J is the rate of transfer of permeant, A is the area of polymer through which diffusion takes place, D is the diffusion coefficient, C is the concentration of permeant in the polymer, and x is the space coordinate measured normal to the cross-sectional area of the polymer.[22] Indeed, even the diffusion of solvating vapors may be described by such a simple formalism in the limit of low activity of concentration of the vapor in the polymer.[23] In such an instance, the sorption of the diffusate at the surface of the polymer will follow Henry's law, which linearly relates the concentration of the penetrant at the surface of the film to its partial pressure, p, adjacent to polymer, i.e.,

$$C = Sp \tag{2}$$

where S is the Henry's law constant, or solubility coefficient. If the film is of thickness ℓ, and its faces at $x = 0$ and $x = \ell$ are maintained at concentrations $C = C_1$ and $C = C_2$, respectively, we can immediately integrate Eq. (1) to get an expression for the steady-state flow of diffusate through the polymer. Thus,

$$J_{ss} = D\frac{(C_1 - C_2)}{\ell} \tag{3}$$

where J_{ss} now refers to the steady-state flux, the rate of penetrant flow per unit area of polymer. It is clear from the above expression that the steady-state concentration gradient is a linear one.

Rearranging Eq. (3) to solve for D, the diffusion coefficient, yields

$$D = \frac{J_{ss}\ell}{(C_1 - C_2)} \tag{4}$$

Thus, if the quantities on the right-hand side of Eq. (4) are known or can be measured it is a simple matter to obtain the Fick's law diffusion coefficient. Frequently, however, it is impossible to measure surface concentrations directly; nevertheless, the partial pressure of permeant at the film surface is

usually known, and when Eq. (2) is substituted into Eq. (3), the resulting expression is

$$J = P\frac{(p_1 - p_2)}{\ell} \tag{5}$$

in which the product of the diffusion and solubility coefficients is replaced by P, the permeability coefficient. The term P describes the overall permeation process while S characterizes the sorption of permeant at the polymer surface and D, its passage through the matrix.

While Eq. (3) expresses steady-state flow, the transient diffusion of the permeant may be described by Fick's second law which, for a diffusion coefficient independent of penetrant concentration, is given by

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{6}$$

The solution to Eq. (6) depends on the boundary conditions of the problem. In most studies of diffusion in polymers, it is quite common to expose a film, initially free of permeant, to a constant concentration or activity of gas at one face ($x = 0$) and then monitor the quantity of penetrant diffusing through the opposite surface, ensuring at the same time that the concentration at the downstream surface is negligible compared to the upstream concentration. Under such experimental constraints, the boundary conditions may be expressed mathematically as

$$C(x,0) = 0 \tag{7}$$

$$C(0,t) = C_1 \tag{8}$$

$$C(\ell,t) = 0 \tag{9}$$

The solution to Eq. (6) subject to the constraints defined above is

$$C(x,t) = -2\sum_{n=1}^{\infty}\frac{2C_1}{n\pi}\exp\left(\frac{-n^2\pi^2 Dt}{\ell^2}\right)\sin\frac{n\pi x}{\ell} - \left[C_1\frac{x}{\ell} - C_1\right] \tag{10}$$

and when this result is substituted into Eq. (1), we arrive at the following expression for the time-dependent penetrant flux:

$$J(t) = J_{ss}\left[1 + 2\sum_{n=1}^{\infty}(-1)^n\exp\left(\frac{-n^2\pi^2 Dt}{\ell^2}\right)\right] \tag{11}$$

If, for the polymer-penetrant system under investigation, the assumptions implicit in the derivation of Eq. (11) are valid; then Eq. (11) gives the response of the polymer film to a step change in penetrant concentration at one of its surfaces.

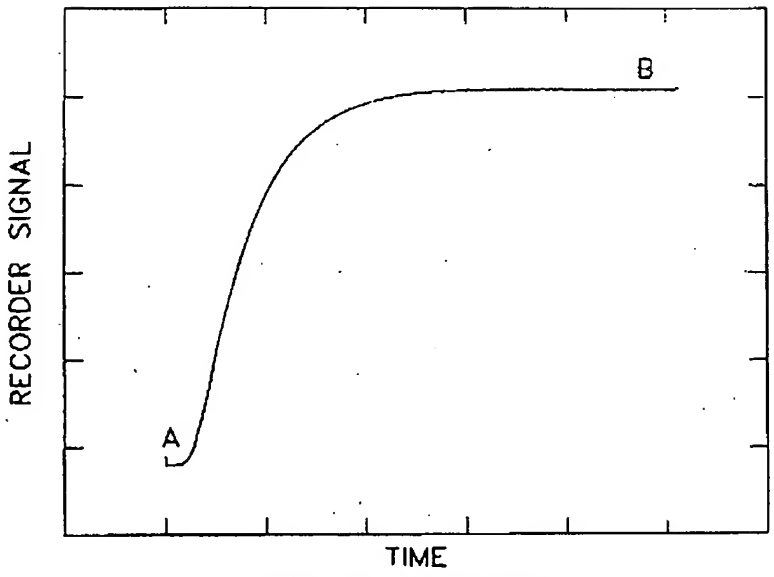

Fig. 1. Typical recorder trace.

CARRIER GAS METHOD OF MEASUREMENT

Numerous techniques for determining the transport parameters of gases and vapors in polymers exist, and they have been discussed in an extensive review by Lomax.[24,25] Of these experimental methods those that fall under the general heading of partition-cell methods have proven quite popular with workers in the field of transport in polymers. Although one particular partition-cell method, the high vacuum technique of Barrer,[26] has been the classical method of studying permeation through polymer films and membranes, in the last 20 years the carrier gas method or dynamic flow technique has been introduced as an alternative to it.

The carrier gas method was first conceived in the early 1900s[28] but was "reinvented" about 20 years ago.[9] In its simplest form, the carrier gas approach uses two streams of gas, both at nearly atmospheric pressure, flowing across each surface of a flat film or membrane which is clamped in a special permeability cell. Permeant gas or vapor is passed through the upstream chamber of the cell, while in the downstream compartment, flowing carrier gas picks up any permeant that has diffused through the polymer and transports it to a detector. The detector signal should be proportional to the permeation rate and hence to the penetrant flux [Eq. (11)]. It can be measured by an analog recorder or computer, for example, and the progress of the experiment can be conveniently monitored.

Figure 1 shows a typical recorder trace that might be obtained during the course of the permeation measurement. At point A, permeant is introduced into the system. The portion of the sigmoidal curve labelled AB represents the transient response of the system. At point B the steady-state concentration gradient has become fully developed and the flux remains invariant as long as the boundary conditions [Eqs. (8) and (9)] are maintained. Analysis of the

transient portion of the curve yields the diffusion coefficient while the permeability coefficient may be calculated knowing the steady-state flux of penetrant.

The carrier gas approach described above has the following advantages over the high vacuum technique of Barrer:

Since the permeability cell operates at or near atmospheric pressure on both sides of the film, little or no support for the polymer is required.

Operation at atmospheric pressure simulates conditions under which many plastic films are used. Packaging films are an example.

Simplicity of design and operation at atmospheric pressure largely eliminate the problem of leaks in the system.

MATHEMATICAL TREATMENT OF EXPERIMENTAL RESULTS

The calculation of permeability coefficients from the recorder trace shown in Figure 1 is quite straightforward. Once the detector has been calibrated with known concentrations of penetrant, the steady-state signal can be converted to the steady-state permeation rate. Then, knowing the film thickness and the difference in penetrant partial pressure across the film, P may be calculated by rearranging Eq. (5). There are, however, several means by which the transient part of the permeation curve may be analyzed to elicit the diffusion coefficient.[10,11,13,15,28] We have used only two of them.

The simpler of the two methods is known as the half-time method, and it was first outlined by Ziegel, Frensdorff, and Blair.[10] If $t_{1/2}$ denotes the time required for the penetrant flux to reach half its steady-state value, then $J/J_{ss} = 1/2$ at $t = t_{1/2}$. Substituting this into Eq. (8) and solving for D, we obtain

$$D = \frac{\ell^2}{7.2t_{1/2}} \tag{12}$$

In most carrier gas systems there is a finite amount of time required for the penetrant gas or vapor to reach the surface of the film from its source. As well, the carrier gas-penetrant mixture also requires a certain amount of time to flow from the downstream side of the permeability cell to the detector. Thus, the half-time obtained from the recorder trace, $t'_{1/2}$, must be corrected for these time lags. An estimate of the "true" half-time, $t_{1/2}$, may be obtained by subtracting from $t'_{1/2}$ all time lags. Such a procedure amounts to shifting the recorder trace or permeation curve along the abscissa. The sum of the lags may be determined by measuring the time required for a signal to be recorded when a step change in concentration is introduced on one side of a metallic film containing a pinhole.[28] Alternatively, the lags may be estimated by summing up the residence time of the gas or vapor in the various system components.

In the second method, known as the method of moments,[15,29,30] the time-varying signal of the detector is not considered as a measure of the response of the polymer film to a step change in concentration. Instead, it considers the resulting signal a measure of the response of the entire system to the unit step

input. The contribution of the other components (the cell, the detector, and the connecting tubing) can be factored out, thereby isolating the response of the film alone. From this response, the diffusion coefficient may be calculated by an equation similar in form to Eq. (9). The characteristic time in this method, denoted M_o, is calculated by integrating the quantity $1 - J/J_{ss}$ from $t = 0$ to $t = \infty$. Because of the time lags inherent in the system, however, $J(t)$ is not equivalent to $R(t)$, the instantaneous detector signal. Hence, a quantity analogous to M_o which represents the characteristic time of the entire system must first be calculated. This quantity, M_o', is given by

$$M_o' = \int_0^\infty (1 - R(t)/R_{ss})\, dt \tag{13}$$

where R_{ss} is the asymptotic value of the recorder signal. The contribution of all the system components except the polymer may then be factored out by simply subtracting the value of their time lags from M_o', thereby leaving only the pure lag due to polymer. Thus

$$M_o = M_o' - \Sigma\tau_i \tag{14}$$

where $\Sigma\tau_i$ represents the sum of the lags due to the connecting tubing, the compartments of the permeability cell, and the lag inherent in the detector itself. Felder et al.[29] provide a theoretical basis for the deconvolution and show that lags due to tubing and compartments are simply the residence times of the permeant gas or vapor in those components. The detector lag is usually small compared to the other delays in the system although it can also be estimated.[29] Moreover, it has also been shown that M_o is equivalent to the time lag, θ, of the Barrer high vacuum method. Thus, the expression for the diffusion coefficient is simply

$$D = \frac{\ell^2}{6M_o} \tag{15}$$

Once P and D have been calculated, the Henry's law solubility coefficient, S, may be determined by calculating the ratio of the permeability and diffusion coefficients.

EXPERIMENTAL DETAILS

Materials

All gases and gas mixtures were obtained from the Linde Division of Union Carbide Limited. The carrier gas was helium with a purity greater than 99.996% and an oxygen content not exceeding 3 ppm. For calibration of the detector and for experimental runs, mixtures of ethylene oxide in helium were used. Mixtures with an EtO concentration greater than 50 ppm were made to a tolerance of ±5% while those containing less than 50 ppm were made to ±3%.

The polymer films used in this study were obtained from three different sources. Polyethylene films of three different densities [linear low (LLDPE), medium (MDPE), and high (HDPE)] were obtained from DuPont Canada (Kingston, Ontario) as was the polyvinylchloride film (PVC), although its origin is uncertain. The Teflon-FEP (TEF-FEP) copolymer film was taken from existing stocks in this laboratory and had been originally supplied by the

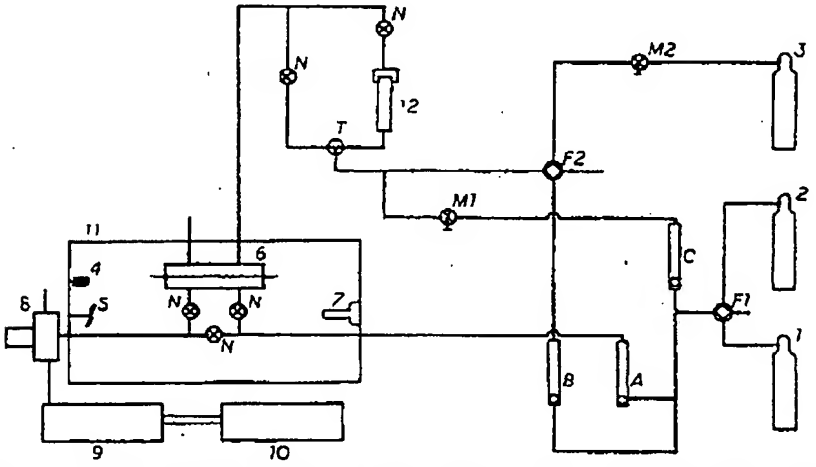

Fig. 2. Permeation apparatus: (A, B, C) high precision rollers; (F1, F2) four-way valves; (M1, M2) metering valves; (N) needles; (1) Helium supply; (2) calibration mixture; (3) permeant gas; (4) 150W light bulb; (5) circulating fan; (6) permeability cell; (7) temperature controller; (8) photoionization detector; (9) electrometer/power supply; (10) stripchart recorder; (11) insulated box; (12) mixing tube.

Plastics Department, Fluorocarbon Division of E. I. DuPont de Nemours and Company, Inc. (Circleville, Ohio). Polypropylene (PP) sheet was supplied by the film division of Mobil Chemical Canada, Ltd. (Belleville, Ontario). All films were nominally 0.0025 cm thick with the exception of the PVC film which was 0.002 cm thick and the high-density polyethylene film which was 0.0019 cm thick.

Apparatus

The carrier gas apparatus in our laboratory, shown schematically in Figure 2, is based on designs described in the literature.[9,11,28] The permeability cell consists of two pieces of type 304 stainless steel, each having a 2-inch diameter, circular recess machined into its surface. When a test film is inserted into the cell, two compartments are formed. Each compartment has a volume of approximately 1 cm^3. Surrounding the lower cavity is an O-ring of Buna-N rubber, which seals the cavities and prevents leaks into or out of the cell. The area of the film exposed to permeant is not defined by the O-ring, however, but by the edges of the cavities. When the cell is clamped shut a metal-film-metal seal is formed. Four corner-bolts pass through both halves of the cell, and uniform compression is provided by tightening wing nuts at each corner. In each cavity inlets and outlets for gas flow are placed as far apart as possible so efficient sweeping of both surfaces of the film can take place.

The entire cell and a portion of the lines leading to and from it were enclosed by a thermostatted oven. The oven consists of a double-walled, insulated box constructed of heavy gauge aluminum sheet. Internal temperature was regulated by a temperature regulator connected to a low wattage heater, which in this case was a 150 W light bulb. A small fan provided the necessary air circulation. This simple design gave remarkably good tempera-

ture control (±1°C) up to 60°C. During the experiments the temperature inside the oven was monitored by a copper-constantan thermocouple.

All gas lines were made of 1/8 in. OD stainless steel tubing. Flows were monitored by Matheson Ltd. and Broods Ltd. precision flowmeters fitted with high accuracy valves. Fittings connecting the tubing to the various components were commercially available compression type. The mixing tube shown in Figure 2 (item 12) consists of a four-inch length of 1 in. OD type 316 stainless steel pipe packed throughout with 3 mm glass beads. Its void volume, measured by filling the tube with water, was approximately 23 cm^3. When ethylene oxide standards were diluted with pure carrier gas the resulting mixtures were sent through the mixing tube to ensure thorough comingling.

The outflow from the lower compartment of the cell is connected directly to a photoionization detector (PID) (HNU Systems Inc., PI 52-02). In the photoionization detector, ionization takes place in a disc-shaped chamber, one face of which is the window of a sealed lamp which emits monochromatic radiation in the ultraviolet (UV) range. A molecular species having an ionization potential less than the energy of the UV lamp will be ionized upon passing through the chamber. The ions resulting from this photoionization are driven to a collector electrode by applying a positively biased high voltage, and the current produced is directly proportional to the concentration of that species.[31] In practice, the PID will detect molecules with an ionization potential (IP) up to 0.3 eV greater than the lamp energy. Thus, to detect EtO (IP = 10.565 eV) lamps with energies of 10.2 eV and 11.7 eV were used.

The PID was coupled to an HNU electrometer/power supply (EPS) which supplied the necessary high voltage for firing the UV lamp and accelerating the ions to the collector electrode. The EPS also contained a rheostat for adjusting the power to the detector and a pyrometer for reading the detector temperature. Lamp intensity could be adjusted from the EPS unit. As intensity was increased, sensitivity increased as well, although only at the cost of greater baseline instability. During the course of a run the detector signal was recorded continuously on a Watanabe CH1 recorder set at 10 mV full scale deflection.

Procedure

Detector Calibration

The photoionization detector was calibrated with standards of EtO in helium which ranged in concentration from 1 to 1000 ppm. It showed a linear response with ethylene oxide concentrations between 3 and 1000 ppm. Below 3 ppm the detector response was only slightly nonlinear, while well above 1000 ppm, severe quenching of the detector signal occurred. Figure 3 shows the response of the PID with the 10.2 eV lamp up to 100 ppm.

Transport Measurements

Films were cut into strips of roughly 8 cm by 12 cm and then carefully examined for macroscopic defects. If the sample was creased, pitted, or contained any other readily visible flaws it was discarded. Prior to an experimental run the test strip was first rinsed with deionized water and then

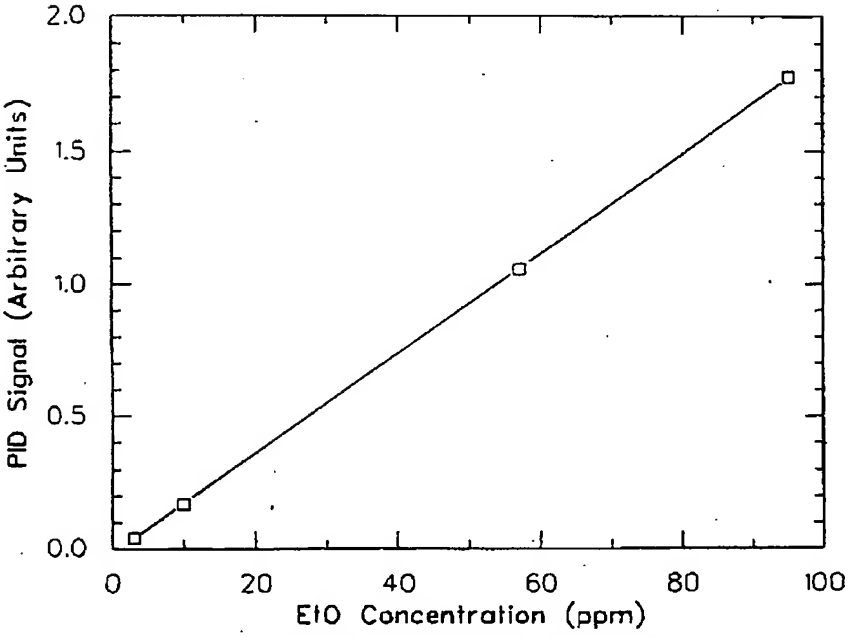

Fig. 3. Calibration curve for PID with 10.2 eV lamp.

vacuum-dried at room temperature for, on average, two hours. It was then placed in the cell and flushed with helium for another four to six hours.

Once the detector and cell temperature had stabilized, the flow of penetrant to the polymer could be initiated by switching the four-way valve labelled F2 in Figure 2. The flow from the penetrant tank was regulated by the metering valve M2, and could be set before the run by attaching a soap bubble flowmeter to the exhaust port of the four-way valve. The carrier gas flow rate was also monitored with a soap bubble flowmeter before an experiment and intermittently during it.

The permeant used was a mixture of ethylene oxide in helium. Pure helium swept the downstream surface of the film. Steady-state flow of ethylene oxide was presumed when the recorder signal remained invariant for three to five minutes.

Calculations

Permeability, diffusion, and solubility coefficients were calculated by the methods outlined earlier. The value of M_∞' was calculated by first determining the value of the integral $\int_0^\infty (R_{ss} - R(t))\,dt$ and then dividing by R_{ss}. Integration was carried out graphically by using a Keuffel and Esser Model 62-0005 Compensating Plane Polar Planimeter.

RESULTS AND DISCUSSION

In one of the few published studies of EtO transport in polymeric films, Waack et al.[32] found that permeability coefficients were dependent on per-

meant concentration. The range of EtO partial pressures to which the films were exposed extended from 8 cm Hg to 35 cm Hg. The passage of organic vapors and liquids through polymeric materials is frequently characterized by such concentration-dependent transport. Nevertheless, it has been shown that in the limit of low penetrant activity, even the diffusion of solvating vapors can be described by concentration-independent Fickian diffusion.[28] Many authors have made use of this mathematically and experimentally advantageous situation when making transport measurements.[28,30,32] Thus, in this study, the maximum partial pressure of EtO to which any of the films was exposed was about 0.76 cm Hg. The permeant gas consisted of a mixture of roughly 1% ethylene oxide in helium.

Effect of Concentration

A single permeation rate experiment, unlike its sorption counterpart, cannot verify the assumption of concentration-independent diffusion directly. It is necessary to measure and compare transport parameters over a range of permeant concentrations or partial pressures.

According to the method of Duncan et al.[30] if a plot of steady-state penetrant flux versus p/ℓ for a particular film is linear, then the ideal solution-diffusion model can be assumed, and the slope of the line will be the permeability coefficient P. The mathematical formulation is

$$J_{ss} = P\frac{p}{\ell} \tag{16}$$

in which the partial pressure difference across the film is given by the partial pressure of the EtO in the permeant gas because the concentration at the downstream surface of the film is zero. Figure 4 shows that such a relationship holds for the permeation of EtO through 0.0019-cm thick high-density polyethylene at 30°C. The slope of the least-squares fitted line, P, is 18.5×10^{-10} cm^3 (STP) cm/s cm^2 cm Hg. The concentrations at the extremities of the abscissa represent commercially prepared mixtures of 1080 ppm and 10,200 ppm while intermediate values represent mixtures made by diluting a stream of 1.02% EtO in helium with pure carrier gas to achieve the approximate desired concentrations. Hence, for this high-density polyethylene film, diffusion can be described by concentration-independent Fickian diffusion between approximately 0.07 cm Hg and 0.7 cm Hg. It is likely that this behavior extends to the other polyethylene films.

None of the other films could be tested in a like manner because of their low permeabilities. Thus, although it can be presumed that transport through PVC, PP, and Teflon-FEP copolymer films is concentration independent because of the low penetrant concentration encountered, the results for these films should be used with caution, keeping in mind the conditions under which the measurements have been made.

Permeability Coefficients

Permeability coefficients were measured for the six films over a 30 Celsius degree temperature range. The linearity of the Arrhenius plots in Figures 5 and 6 indicate that within the temperature range shown (approximately

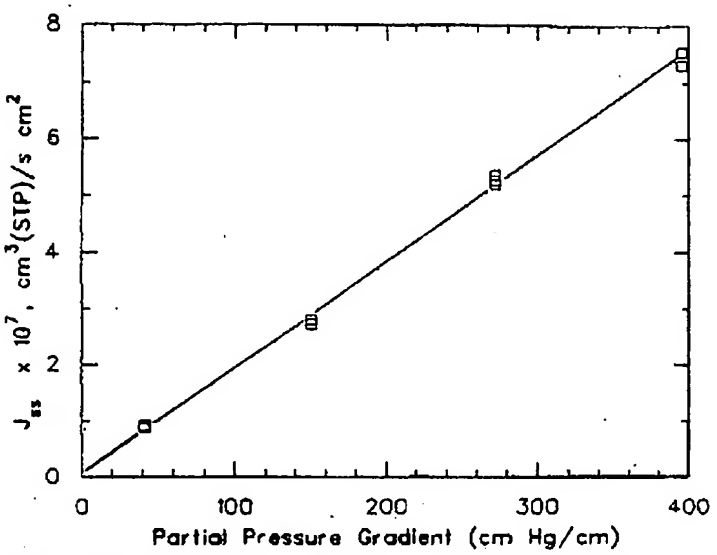

Fig. 4. Effect of EtO partial pressure on steady state flux. (0.0019 cm HDPE.)

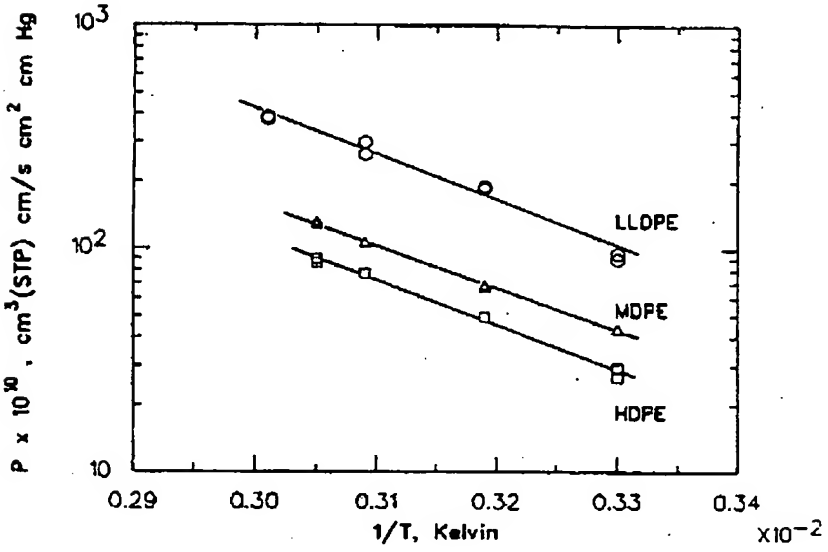

Fig. 5. Arrhenius plot of EtO permeability coefficients. (Polyethylene Films.)

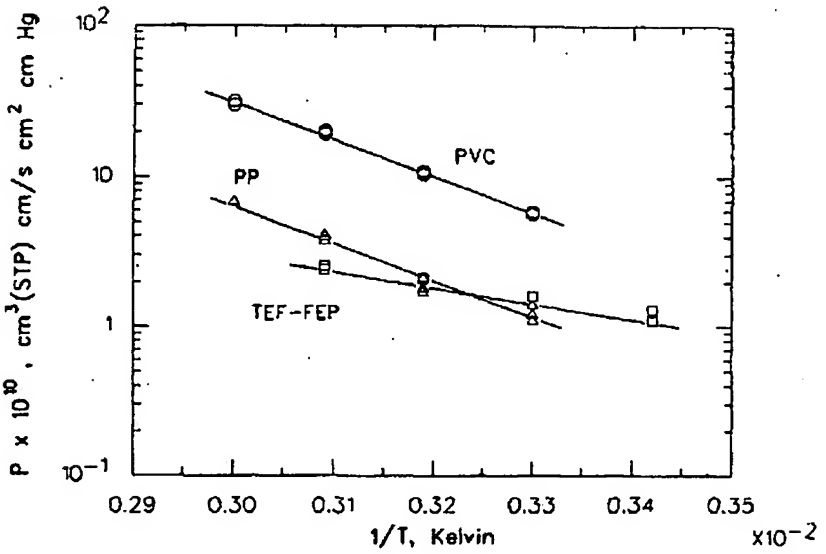

Fig. 6. Arrhenius plot of EtO permeability coefficients. (PVC, PP, and TEF-FEP.)

20°C–60°C), the process of permeation can be satisfactorily described by the expression

$$P = P_o \exp(-E_p/RT) \tag{17}$$

P_o, the pre-exponential factor, and E_p, the activation energy for permeation, are listed in Table I along with permeability coefficients at 30°C.

Waack et al.[32] determined the permeability coefficient of EtO in several films at various partial pressures. At a partial pressure of 8.1 cm Hg, the lowest value at which transport measurements were made, the permeability of EtO through low-density polyethylene film we reported to be 22×10^{-10} cm^3

TABLE I
Permeability Data for Ethylene Oxide

Films	$P \times 10^{10}$ (30°C) $\frac{\text{cm}^3\ (\text{STP})\ \text{cm}}{\text{s cm}^2\ \text{cm Hg}}$	P_o	E_p cal/mol	% Crystallinity[a]
LLDPE	91.8(20)[b]	.135	9890	31.2
MDPE	43.1(20)	.007	8650	38.8
HDPE	28.5(20)	.011	9130	46.6
PVC	5.8(10)	.073	11150	—
PP	1.2(20)	.039	11750	—
TEF-FEP	1.1(15)	6.7×10^{-7}	4970	—

[a] From differential scanning calorimetry (DSC) measurements.
[b] Figures in parentheses are uncertainties expressed as a percentage.

(STP) cm/s cm^2 cm Hg at 0°C. If the Arrhenius plot for LLDPE (Fig. 5) is extended to 0°C, the apparent permeability coefficient at that temperature is 16×10^{-10} cm^3 (STP) cm/s cm^2 cm Hg.

As a group, the polyethylene films are more permeable to ethylene oxide than the other films studied. In semicrystalline polymers like polyethylene, sorption and diffusion are believed to occur exclusively in the amorphous regions of the polymer.[25] As amorphous content increases permeability should also increase. The data in Table I show that the permeability of the polyethylene films increases as the crystallinity decreases from 46% to 31%. Figure 5 and the data in Table I also show that the activation energy for permeation is roughly the same for low, medium, and high-density polyethylene films. If, indeed, transport does take place solely through amorphous regions then such a similarity would not be unexpected since the amorphous environment is likely quite similar in all three samples.

In some instances the point at which steady-state flow through the polymer was reached was difficult to identify unambiguously on the recorder trace. This difficulty was due primarily to the fluctuation of temperature within the oven surrounding the cell and a slight temperature drift of the detector block. It is partly reflected in the estimates of uncertainty shown in Table I. A more complete discussion of the uncertainties in all the coefficients calculated may be found elsewhere.[36] Precise identification of steady state is important not only in the determination of P, but also in the determination of the diffusion coefficient.

Diffusion Coefficients

For all films except polypropylene, diffusion coefficients were calculated by the two methods outlined above. Diffusion coefficients calculated by the half-time method are denoted D_H while those determined by the method of moments are denoted D_M. Their variation with temperature is shown in Figures 7 to 11. The activation energy for diffusion, E_d, and the pre-exponential factor D_o, derived by fitting an Arrhenius expression to the data, are summarized in Table II. The linearity of the plots confirms that little or no interaction takes place between polymer and penetrant.

The activation energy, E_d, is a fundamental parameter associated with the energy required for hole formation, that is, the energy required to separate the polymer chain segments so that passage of a penetrant molecule can occur. If we consider the glass transition (T_g) temperature of a polymer to be a qualitative measure of chain stiffness, we would then expect that a higher T_g (and hence, greater chain stiffness) results in a higher E_d. Correlating the activation energies shown in Table II with the T_gs of the respective polymers we see that the E_d for diffusion through polyethylene films ($T_g \approx -120$°C) is lower than the E_d for diffusion through PP, PVC, and Teflon-FEP, polymers which have much higher glass transition temperatures. Furthermore, a comparison of diffusion coefficients at 30°C with glass-transition temperatures indicates that as T_g (and hence, chain stiffness) increases, the diffusion coefficient decreases.

The activation energies listed in Table II range from 7 kcal/mol to 15 kcal/mol. Some authors[38,39] have pointed out that anomalous diffusion such

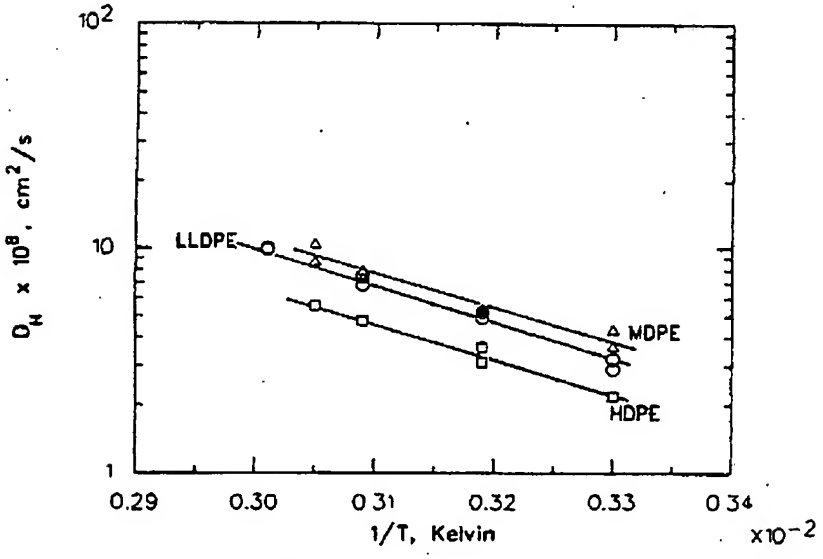

Fig. 7. Arrhenius plot of EtO diffusion coefficients. (D_H, Polyethylene films.)

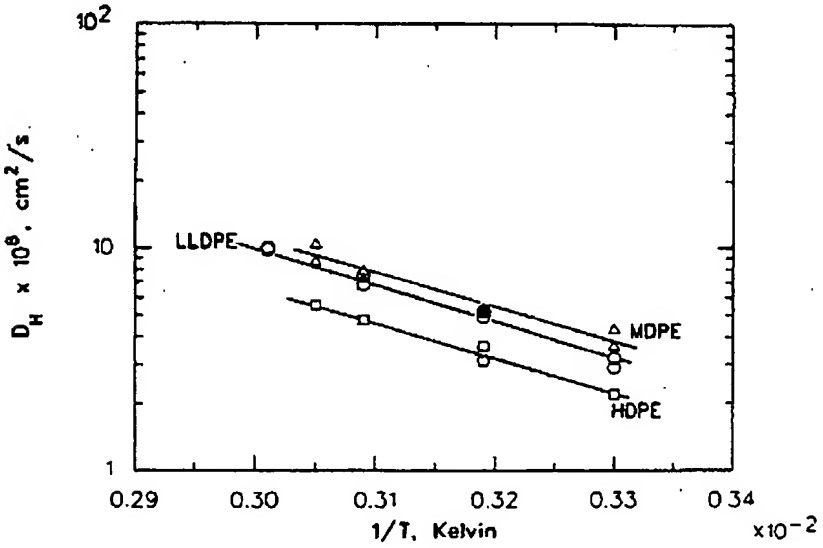

Fig. 8. Arrhenius plot of EtO diffusion coefficients. (D_M, Polyethylene films.)

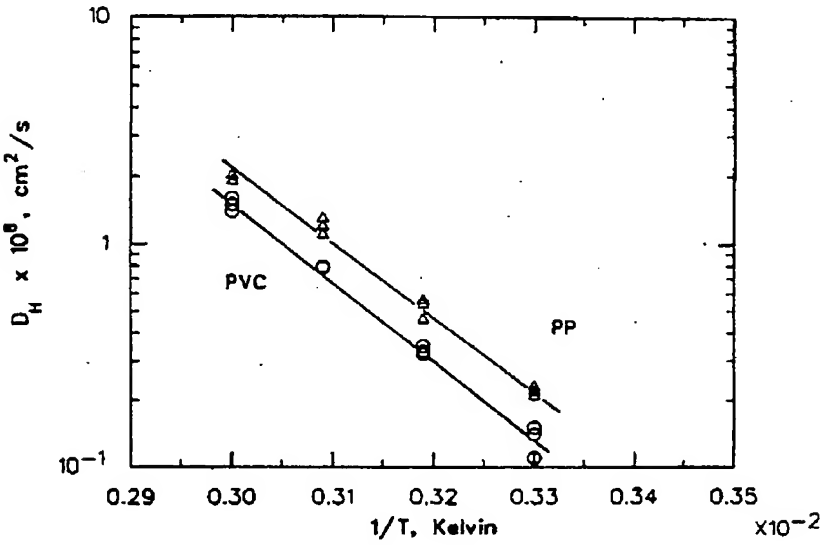

Fig. 9. Arrhenius plot of EtO diffusion coefficients. (D_H, PP and PVC.)

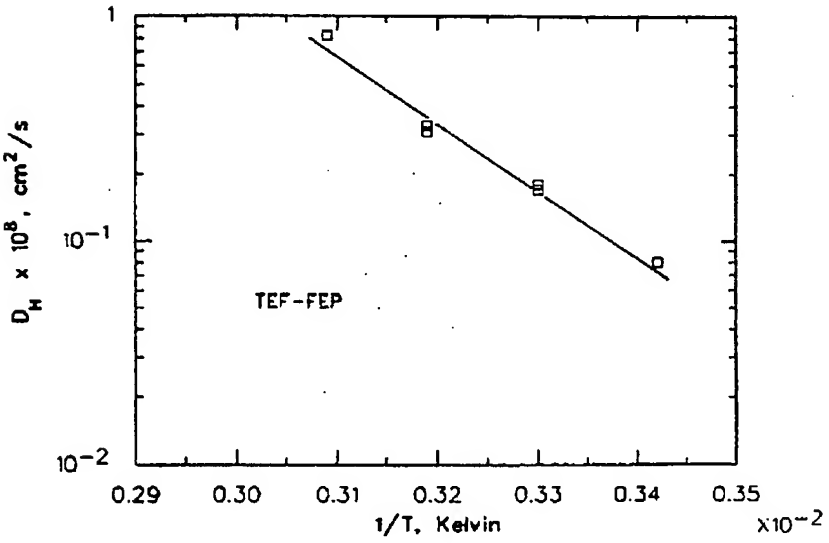

Fig. 10. Arrhenius plot of EtO diffusion coefficients. (D_H, TEF-FEP.)

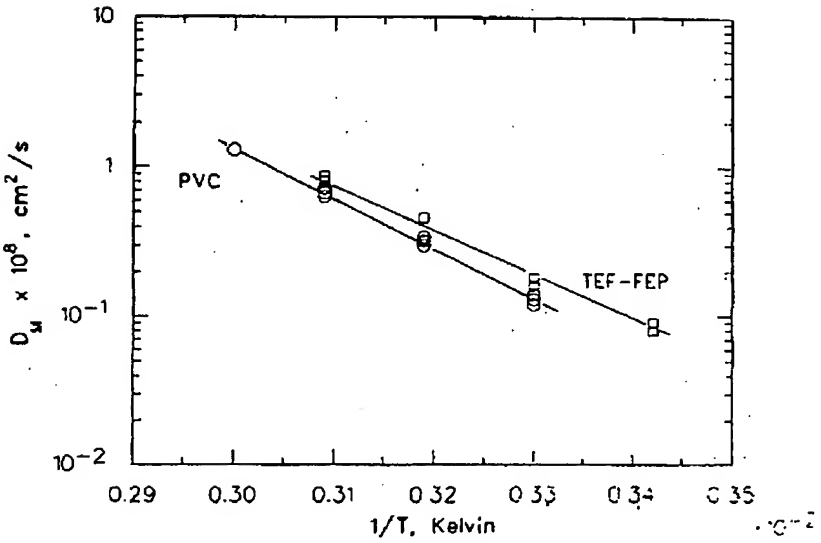

Fig. 11. Arrhenius plot of EtO diffusion coefficients. (D_M, PVC and TEF-FEP.)

TABLE II
Diffusivity Data for Ethylene Oxide

Films	$D_H \times 10^8$ cm²/s (30°C) D_H	D_M	Half-time D_o	Half-time E_d cal/mol	Method of moments D_o	Method of moments E_d cal/mol	T_g °C
LLDPE	3.1(25)[a]	3.2(25)	.0172	7950	.012	7760	
MDPE	3.8(25)	3.6(25)	.0044	7025	.0004	5700	−120[c]
HDPE	2.1(15)	2.3(15)	.0054	7475	.0007	6220	
PVC	.13(15)	.13(10)	642	16180	156	15350	39[b]
PP	.22(20)	—	[illegible]	15000	—	—	−6[b]
TEF-FEP	.17(15)	.17(15)	47	14470	47	14450	126[d]

[a] Figures in parentheses are uncertainties expressed as a percentage.
[b] From DSC measurements; PVC contains unknown amount of plasticizer.
[c] From Ref. 36.
[d] From Ref. 37, T_g of polytetrafluoroethylene.

as Case II diffusion is usually associated with much higher activation energies than Fickian diffusion. Although no range of values appropriate to Fickian diffusion can be distinctly defined, a comparison of the energies in Table II with the data of Stannett[21] reveals that a range of 7–15 kcal/mol corresponds to the activation energy for the diffusion of simple gases in high polymers, a phenomenon which follows the Fickian model.

The E_d values for the polyethylene films are, like the E_p values, nearly equal. There is no observable trend among them, and given the error associ-

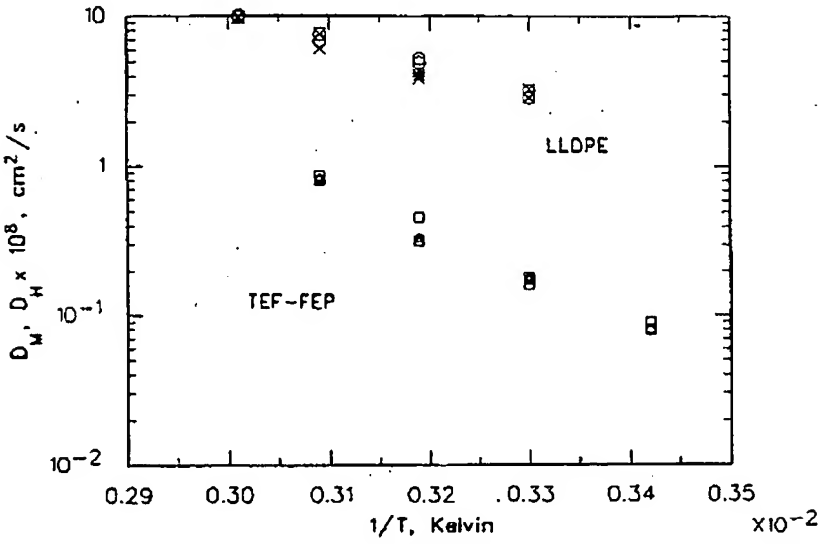

Fig. 12. Comparison of D_H and D_M. (LLDPE and TEF-FEP): (O, △) D_H; (×, □) D_M.

ated with them, it is likely that they are not significantly different from one another. Again, if the environment through which the penetrant diffuses is similar in the three polyethylene films, the activation energies would also be nearly equivalent.

In general, half-time diffusion coefficients agreed well with diffusion coefficients calculated by the method of moments. Values of D_H and D_M at 30°C are shown in Table II for all films except polypropylene, and in Figures 12 to 14 D_M and D_H are shown on the same graph for LLDPE, MDPE, PVC, and TEF-FEP. It can be seen that, within the precision of the data, diffusion coefficients determined by the half-time method and method of moments are not significantly different. Neither method of determining diffusion coefficients, however, deals adequately with the difficulties that arise when the characteristic times, M_o or $t_{1/2}$, are on the same order of magnitude as the equipment lags. For relatively permeable films such as polyethylene at higher temperatures, the characteristic time, M_o or $t_{1/2}$, is of the same order of magnitude as the lags inherent in the permeation equipment. Thus the determination of the diffusion coefficient becomes extremely sensitive to the uncertainty in the value of the time delay. However, for smaller diffusion coefficients, that is, larger characteristic times, the time delay can be ignored. For example, the apparent half-time for the diffusion of EtO in Teflon-FEP at 20°C is about 1000 s. Disregarding the delay of approximately 20 s results in an error of only 2% in the calculated result.

Such observations point to a deficiency in the carrier gas technique. Namely, because of the sensitivity of the diffusion coefficient to the equipment lag with very fast films, the dynamic flow method may be more suited to less perme-

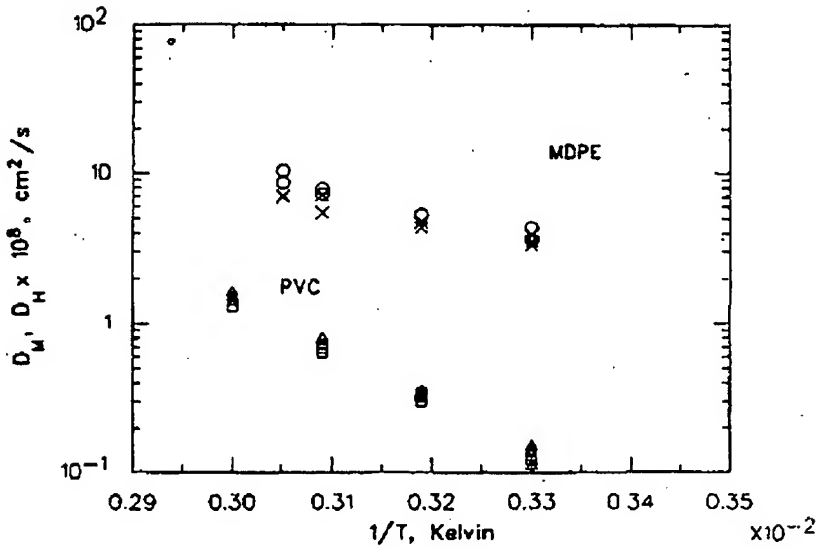

Fig. 13. Comparison of D_H and D_M. (MDPE and PVC): (O, △) D_H; (×, □) D_M.

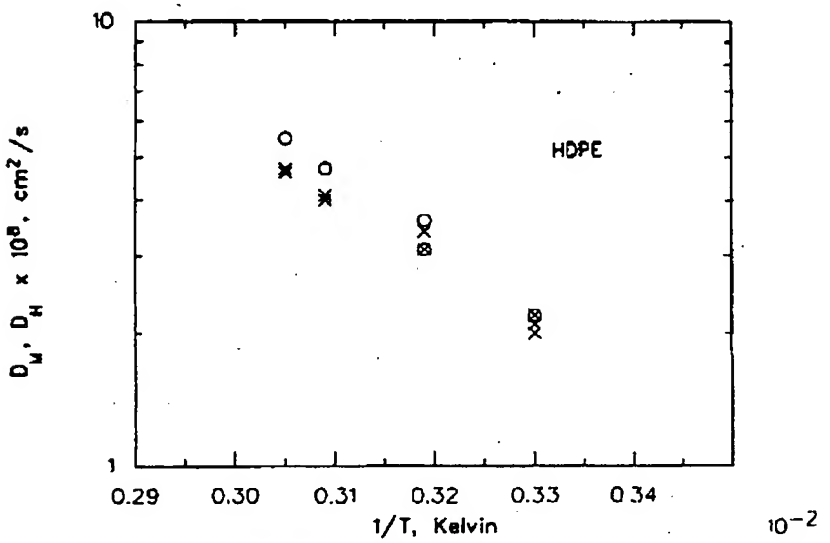

Fig. 14. Comparison of D_H and D_M. (HDPE): (O) D_H; (×) D_M.

TABLE III
Solubility Data for Ethylene Oxide

Films	S (30°C) cm^3 (STP) / cm^3 cm Hg S_L	S_M	Half-time S_o	Half-time ΔH_s (cal/mol)	Moments S_o	Moments ΔH_s (cal/mol)	δ $(cal/cm^3)^{1/2}$
LLDPE	.09[a]	.29(40)	7.8	1940	11.3	2130	
MDPE	..35)	.11(28)	1.7	1620	16.4	2940	7.8[b]
HDPE	.13(25)	.14(25)	2.1	1660	16.8	2910	
PVC	.44(20)	.45(15)	.0001	−5030	.0004	−4200	9.4–10.8[b]
PP	.06(28)	—	.0003	−3250	—	—	8.3[c]
TEF-FEP	.09(20)	.12(20)	2.3×10^{-8}	−9190	1.8×10^{-8}	−9160	—

[a] Figures in parentheses are uncertainties expressed as a percentage.
[b] Ref. 37.
[c] Ref. 36.

able films. At the other extreme, however, detector instability at very high sensitivities over a long period of time makes the method less suitable for highly impermeable films. Other authors[13] have recommended that the carrier gas method be used with moderately permeable films only. Nevertheless, despite misgivings that it is based on a single point, the half-time method is a remarkably robust method which provides estimates of the diffusion coefficient quickly and easily.

Solubility Coefficients

Solubility coefficients were determined by calculating the quotient P/D. Shown in Table III are solubility coefficients at 30°C, along with the parameters obtained by fitting the data to the van't Hoff expression

$$S = S_o \exp(-\Delta H_s/RT) \tag{18}$$

ΔH_s is the heat of solution of penetrant in the polymer and S_o is the pre-exponential factor. Because S is obtained indirectly in most partition-cell methods like the carrier gas technique, the uncertainties in the permeability and diffusion coefficients are both reflected in the error associated with the solubility coefficients. Uncertainties for the six films studied are also listed in Table III. In some instances the resultant errors can be large enough to obscure the effect of temperature on solubility. For example, the correlation between $\log S$ and $1/T$ for polypropylene (Fig. 15) is a poor one. However, given that P and D follow Arrhenius dependencies for PP, and indeed for all other films, scatter in the van't Hoff plots (Figs. 15–19) is probably not due to any sorption anomalies. The heat of solution ΔH_s, obtained from S_H differs markedly with that obtained from S_M, but by examining the relative magnitudes of ΔH_s and S for all films rather than their absolute magnitudes it is still possible to draw some meaningful conclusions.

Chemical similarity between the polymer and sorbate is a major factor determining the extent of solubility. The square root of the cohesive energy density, or δ, its solubility parameter, is frequently used to predict solubility

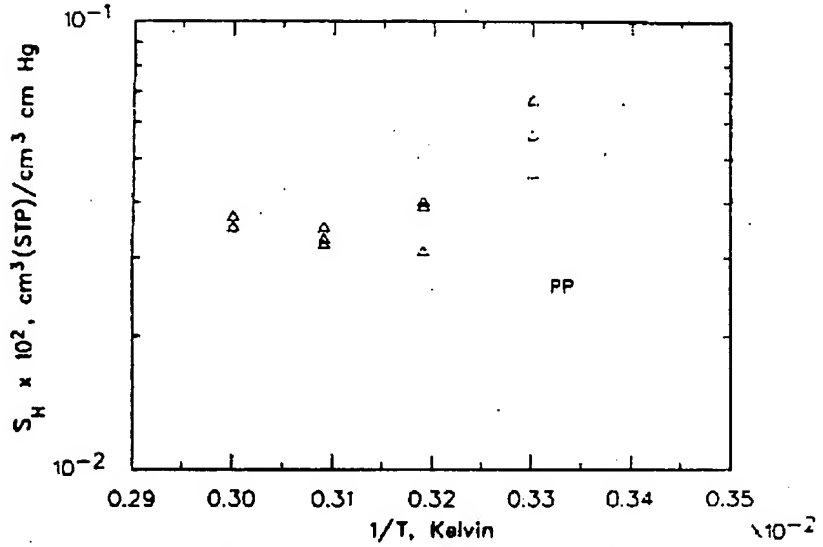

Fig. 15. Van't Hoff plot of EtO solubility coefficients. (S_H, PP.)

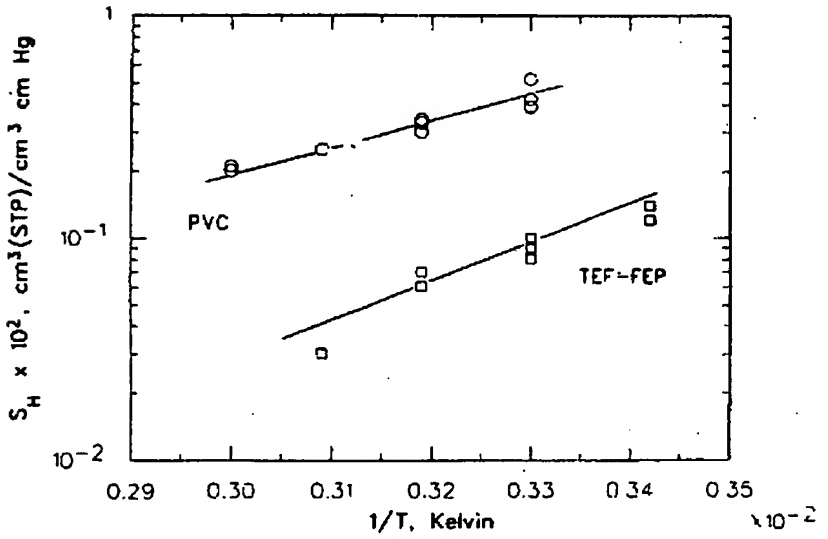

Fig. 16. Van't Hoff plot of HtO solubility coefficients. (S_H, PVC and TEF-FEP.)

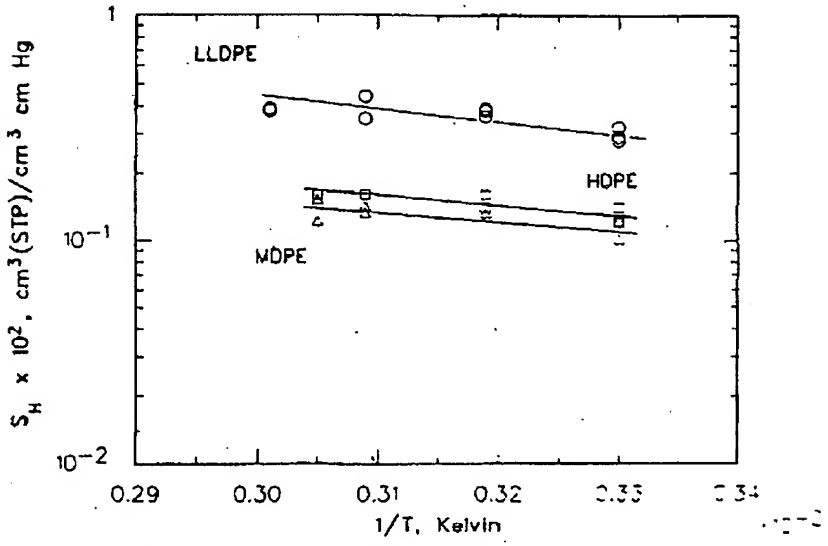

Fig. 17. Van't Hoff plot of EtO solubility coefficients. (S_H, Polyethylene films.)

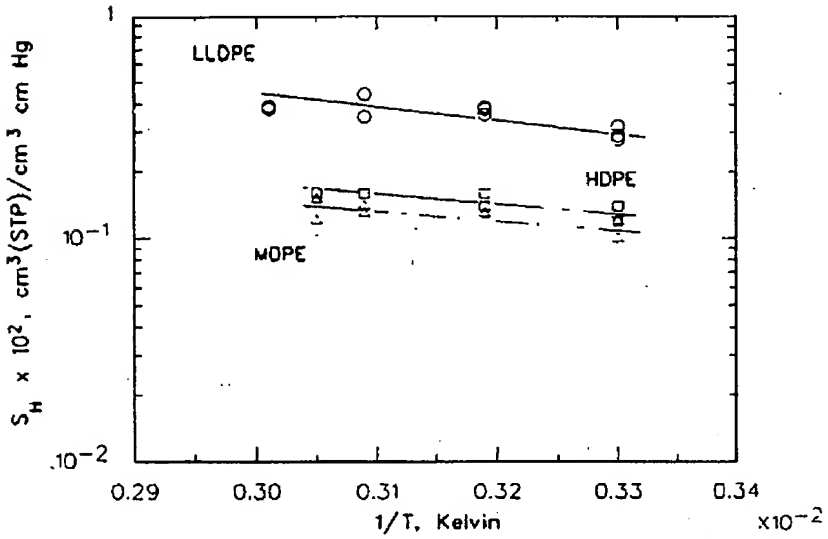

Fig. 18. Van't Hoff plot of EtO solubility coefficients. (S_M, Polyethylene films.)

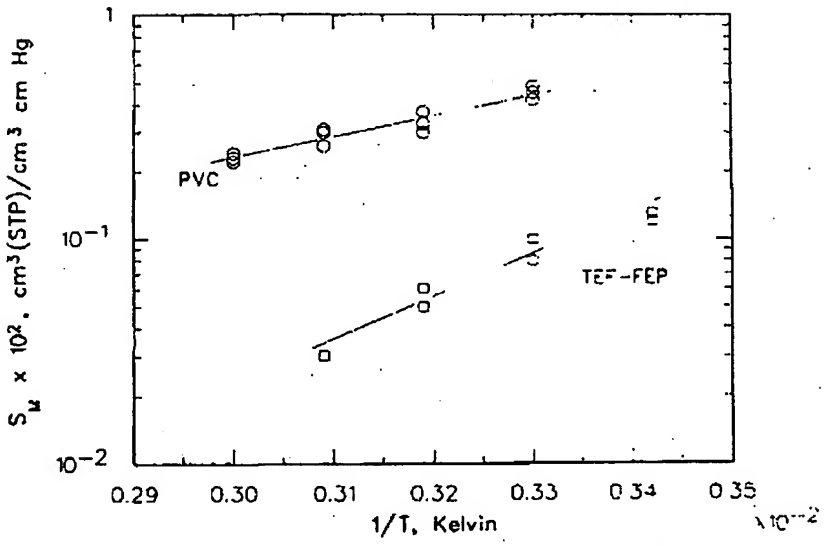

Fig. 19. Van't Hoff plot of EtO solubility coefficients. (S_M, PVC and TEF-FEP.)

and compatibility. As the δ values of a polymer and penetrant become more equal, the solubility of that sorbate should increase. The δ value of EtO is 11.1 $(cal/cm^3)^{1/2}$,[40] and comparing its solubility in PVC and polyethylene in Table III we see that EtO is more soluble in PVC, a polymer whose solubility parameter is numerically closer to 11.1 $(cal/cm^3)^{1/2}$.

The sorption of a penetrant onto the surface of a polymer can be considered as a two-stage process: first, condensation of the vapor followed by mixing of the condensed vapor with the polymer.[41] Associated with the first step is the molar heat of condensation of the permeant, ΔH_c, and with the second step, the partial molar heat of mixing, ΔH_m. Thus,

$$\Delta H_s = \Delta H_m + \Delta H_c \tag{19}$$

The value of ΔH_m can be estimated by means of the Hildebrand equation, i.e.,

$$\Delta H_m = \bar{V}_1(\delta_1 - \delta_2)^2\phi_2^2 \tag{20}$$

The volume fraction of polymer, usually unity in the case of a dilute solution, is denoted by ϕ_2, and $\bar{V}_1$ represents the partial molar volume of the penetrant in the polymer.

For gases well above their critical points, the hypothetical [illegible] of ΔH_c is negligible and therefore ΔH_s is determined by ΔH_m which is positive and usually quite small.[42] Thus, the solubility coefficient increases with temperature. For more condensible vapors and gases the heat of condensation contrib-

utes proportionately more than ΔH_m and solubility decreases with increasing temperature. Heats of solution of EtO in Teflon-FEP, PVC, and polypropylene are negative (exothermic) and solubility decreases as expected with increasing temperature. Heats of solution in polyethylene, however, are positive (endothermic) despite the fact that EtO is a very condensible vapor; its normal boiling point is 10.5°C.[43] Aboul-Nasr and Huang[44] encountered the same phenomenon when studying the sorption of benzene and hexane in modified polyethylene films, and explained it qualitatively in terms of relative changes in segmental mobility of the polymer chains and changes in condensibility. As temperature increases the vapor becomes increasingly less condensible. However, at the same time the segmental mobility increases which allows more vapor molecules to become sorbed at the interface. Depending on which effect predominates, solubility may increase or decrease with temperature. For ethylene oxide in polyethylene, it appears that the decrease in condensibility of penetrant is offset by the large increase in chain mobility.

Between 20°C and 60°C the average heat of condensation of ethylene oxide is about −5700 cal/mol (38). Hence, Eq. (20) reduces to

$$\Delta H_s = -5700 + \bar{V}_1(\delta_1 - \delta_2)^2 \tag{21}$$

if we assume that $\phi_2 \simeq 1$. If the simple two-stage model outlined above is valid, then as the solubility parameters of the polymer and penetrant become more nearly equal the heat of solution becomes, in turn, more exothermic or less endothermic. Table III shows this to be true for four of the six films. Thus, sorption of ethylene oxide in polyethylene and polyvinylchloride can be described, at least qualitatively, by the simple two-stage model and therefore probably follows Henry's law.

A closer examination of Eq. (21) reveals that because the second term is always positive, ΔH_s cannot be greater (more exothermic) than −5700 cal/mol. However, the heat of solution of EtO in Teflon-FEP is approximately −9 kcal/mol, significantly larger than the limiting value prescribed by Eq. (21). When studying the diffusion of isobutane and propane in glassy polycarbonate, Chen[33] also found that the sum of ΔH_c and ΔH_m left roughly −5 kcal/mol of solution enthalpy unaccounted for. He hypothesized that the excess enthalpy could be accounted for by the increased solubility of the permeants in the glassy polymer. The nonequilibrium glass contained excess free volume in the form of microvoids and it was the temperature dependence of this free volume that gave rise to the additional enthalpy. The existence of two modes of sorption (Henry's law sorption and sorption in microvoids) has been described by the dual-mode sorption model.[46] It accounts for the large negative enthalpies of solution in some polymer glasses. The observation here of excess enthalpy in the solubility of EtO in Teflon-FEP bears further investigation to determine the precise nature of the sorption mechanism. If indeed dual sorption occurs, then the solubility coefficients for EtO in Teflon-FEP represent pseudo-Henry's law constants which include contributions from ordinary dissolution and also from microvoid sorption.

CONCLUSIONS

Using a simple apparatus based on the carrier gas method of measurement, estimates of permeability, diffusion, and solubility coefficients describing the transport of ethylene oxide through several polymer films have been obtained. The results indicate that at the partial pressure of EtO to which the films were exposed, diffusion in polyethylene is concentration independent and Fickian. This simple diffusion model is also likely valid for the other films investigated. Two different methods were used to evaluate the diffusion coefficient, and, within the precision of the data, they yield the same results. The observation of excess enthalpy in the solubility of EtO in Teflon-FEP copolymer suggests the possibility of dual-mode sorption, although more work is needed to confirm this.

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